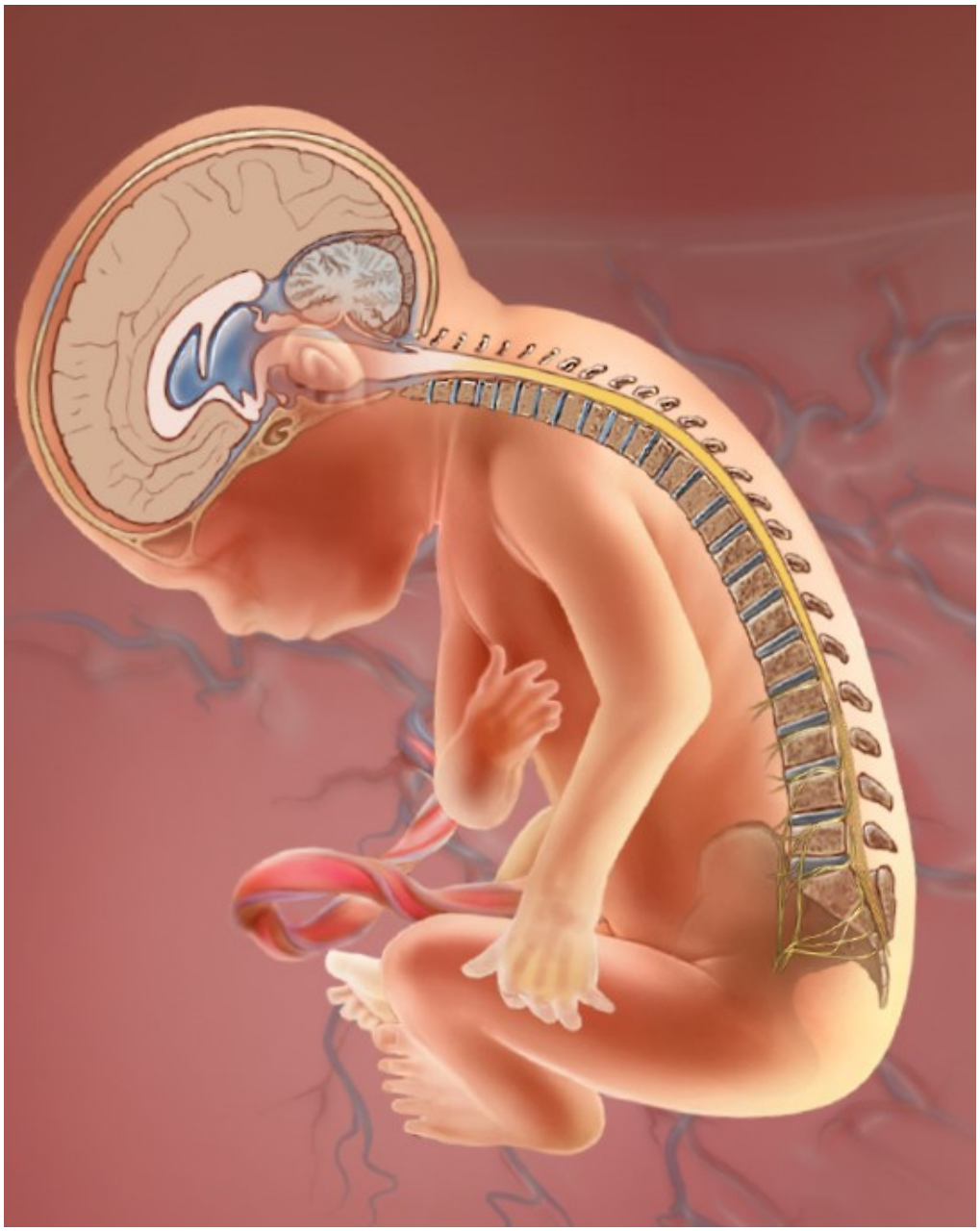
Glossary of

GENETIC

DISORDERS



Dr. Osama Alagamawy Pediatrician

Dedication

To the soul of my mother

A picture is worth 1000 words

(Old Chinese saying)

Golden Role

If there is one congenital anomaly, always look for another.

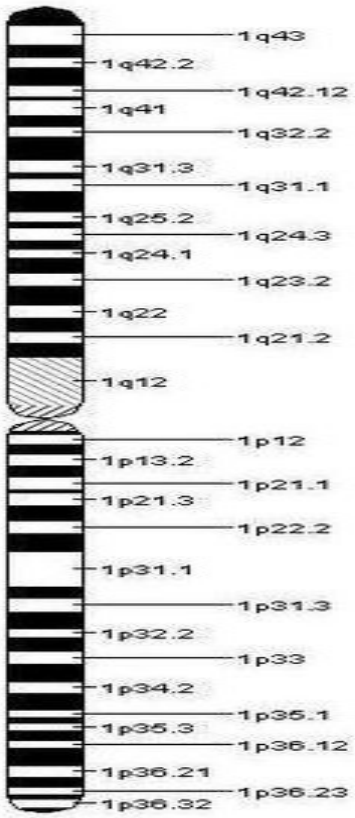
Contents

GENETICS

Introduction

Globally, at least 7.6 million children are born annually with severe genetic or congenital malformation; 90% of them are born in mid and low income countries. Precise prevalence data are difficult to collect, especially in developing countries owing to great diversity of condition and also because many cases remain undiagnosed .The genetic and congenital disorders are the second most common cause of infant and childhood mortality and occurs with a prevalence of 25-60 per 1000 births. The higher prevalence of genetic diseases in a particular community may, however, be due to some social or cultural factors, such as consanguineous marriages, which results in higher rate of autosomal recessive conditions including congenital malformations, stillbirths, or mental retardation. Furthermore, maternal age more than 35 year is associated with higher frequencies of chromosomal abnormalities in the offspring (WHO. 2005), also environmental pollution, wars, chemical weapons, and radiations are very important as it was seen in gulf area after gulf war and the marked rise of congenital malformations especially of bones.

Genes and Human Disease



Chromosome 1

Chromosomes

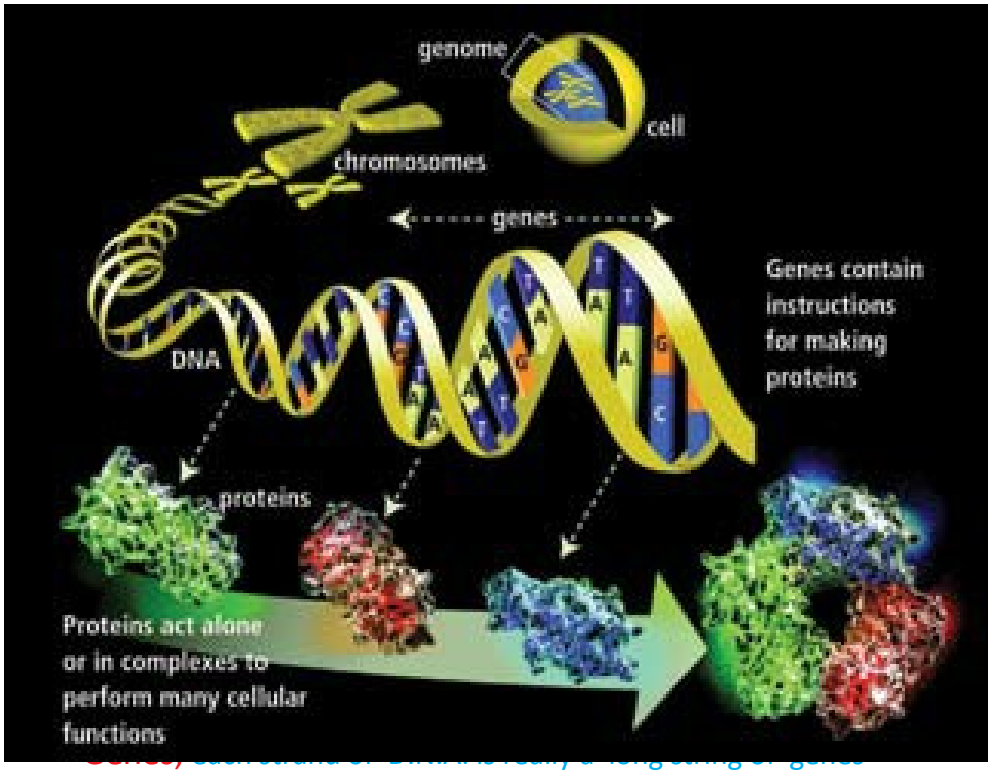
Human body is made-up of trillions of cells, each specializing in particular function and each working together in a complex symphony of interactions, with the exception of red blood cells, which contain no nucleus and no nuclear deoxyribonucleic acid (DNA). Chromosomes are subcellular structures that exist in the nucleus of each cell that makes up the human body, and responsible for transferring genetic information from one generation to another. There are 23 pairs of chromosomes existing in the human cell -22 Autosome + Sex Chromosome known as XY (male) and XX (female). Chromosomes are very long thin strands of DNA coiled up like a ball of string, for example:

Chromosome 1 contain > 3000 genes & 240 million base pairs, of which 90% have been determined.

Chromosome 2 contains > 2500 genes & 200 million base pairs, of which 5% have been determined.

X chromosome contains > 1400 genes & 150 million base pairs, of which 95% have been determined.

Y chromosome contains > 200 genes & 50 million base pairs of which 50 % have be-en determined.



Genes

Are instruction manuals for our bodies. They are the directions for building all the proteins that make our body function. Scientists now think there are 30.000 different human genes in each cell. Over 90% of the genetic code is identical in all of us; there are small variations in DNA between people. It is these small variat-ions that make us all different from each other. Currently estimate that 10.000 of human diseases are known to be monogenic.

CONGENITAL ANOMALIES TYPES

Incidence: 1/100 born baby.

- Chromosomal anomalies: 50 %
- Unknown: 30 %
- Autosomal dominant: 15 %
- Autosomal recessive: 2.5%
- Drug induced: 2.5%

- 2-3% of population are mentally retarded.
- Cause identified in 50-60 % of cases.
- Commonest causes of congenital anomalies (genetic base):

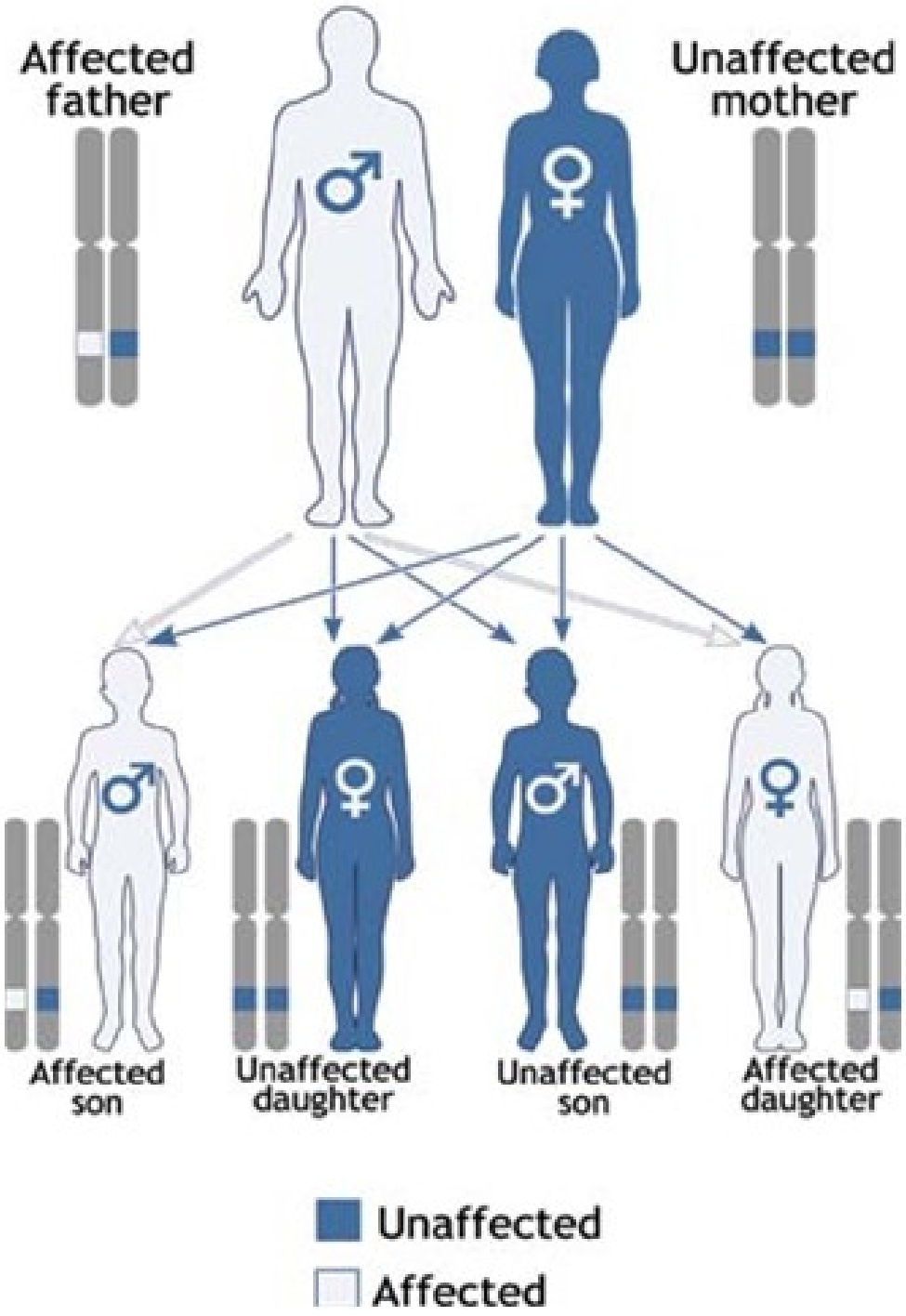
  Down syndrome: 17 %

  Fragile X syndrome: 3 %

  Inborn errors of metabolism: 2 %

AUTOSOMAL DOMINANT DISORDERS

- An affected person usually has at least one affected parent.
- Disorder affects either sex and can be transmitted by either sex.
- Affected person has 50 % chance of passing the defect on to their children.
- Each child have 50% chance to have the disease.



Autosomal Dominant

VON WILLEBRAND DISEASE

Chromosome 12, Gene VWF, Location p13.3

Named after Dr. Erik Adolf Von Willebrand, a Finnish paediatrician in, 1926

Incidence: 1 / 100 population.

- Deficiency of von Willebrand factor (VWF).
- Presented with, epistaxis.
- Mucocutaneous bleeding.
- Skin bleeding.
- Women may experience heavy menses or excessive blood loss during labour.
- Low factor VWF, and factor VIII.
- Prolonged partial thromboplastin time, and bleeding time, thrombocytopenia, and abnormal platelet aggregation .

Desmopressin.

NOONAN SYNDROME

Chromosome12,Gene PTPN11, Location 12 q 24

Named after, Jacquline Noonan, Paediatric Cardiologist, U.SA .in 1968.

It`s believed to be the male version type of Turner syndrome.

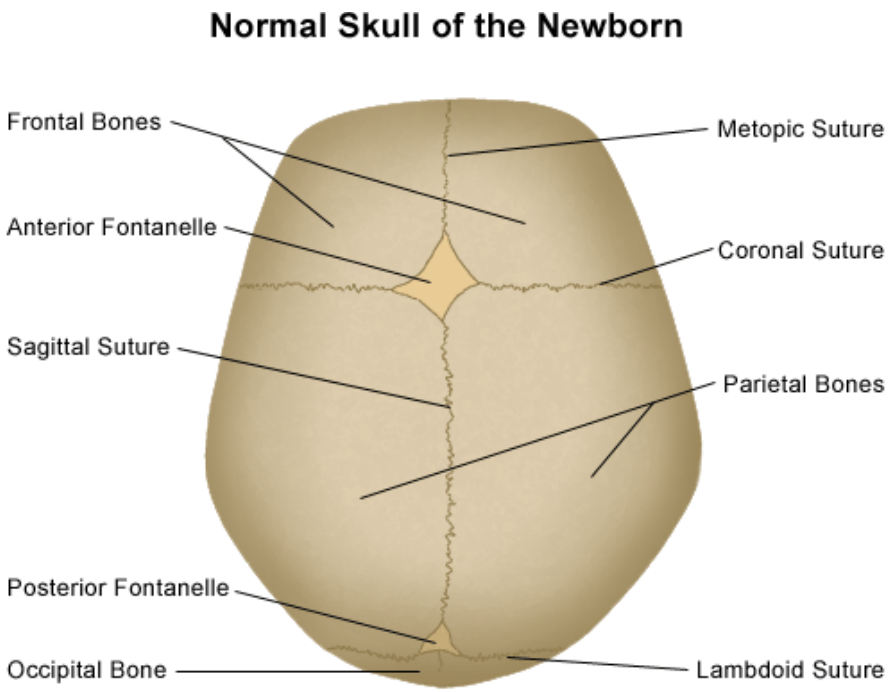
Incidence: 1 / 1000 Births .

- Delayed milestones, short stature, hypotonia.
- Webbed neck.
- Microganthia.
- Low set ears.
- Cubitus valgus .
- Strabismus.
- High hairline at front of head.
- Cryptorchidism.
- Congenital heart disease. (V.S.D. or A.S.D.).

CRANIOSYNOSTOSIS

Chromosome 7, Location 7p 21

Cranio = cranium, syn = together, ostosis = related to bones.

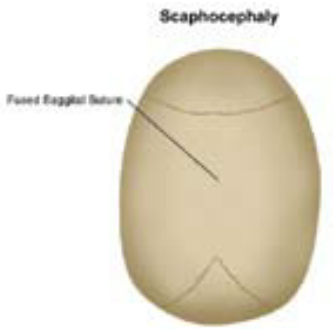


Incidence 1/ 2000 Births.

Premature closure of one or more of cranial sutures, too soon in utero, distu-rbing the normal growth pattern of skull and facial bones.

SCAPHOCEPHALY

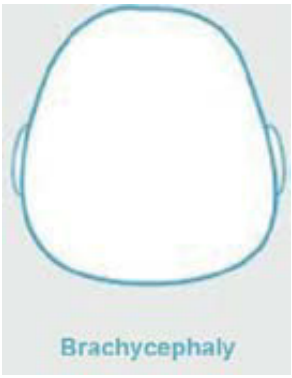
Fusion of sagittal suture.



Scaphocephaly, elongated head and prominent forehead

BRACHYCEPHALY

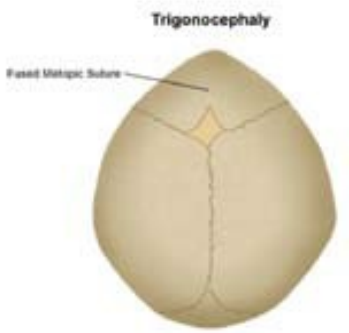
Fusion of coronal suture.



Brachycephaly: Flattening of the head

TRIGONOCEPHALY

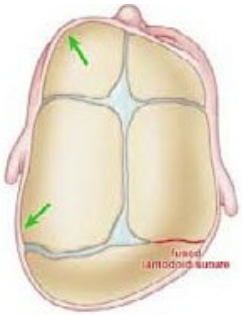
Fusion of metopic suture.



Trigonocephaly: triangular shaped head and eyes appeared very close

PLAGIOCEPHALY

Fusion of Lambdoid suture



Plagiocephaly: Asymmetry of the head and ears are not aligned

CHARCOT MARIE TOOTH DISEASE

Genes TRPV 4 .MPZ or CMTA 1, Location 1 q 23.3

Named after, Jean Martin Charcot, Pierre Marie, Hiward Tooth, England 1886

Charcot Marie Tooth Disease

Incidence : 1 / 2500 people.

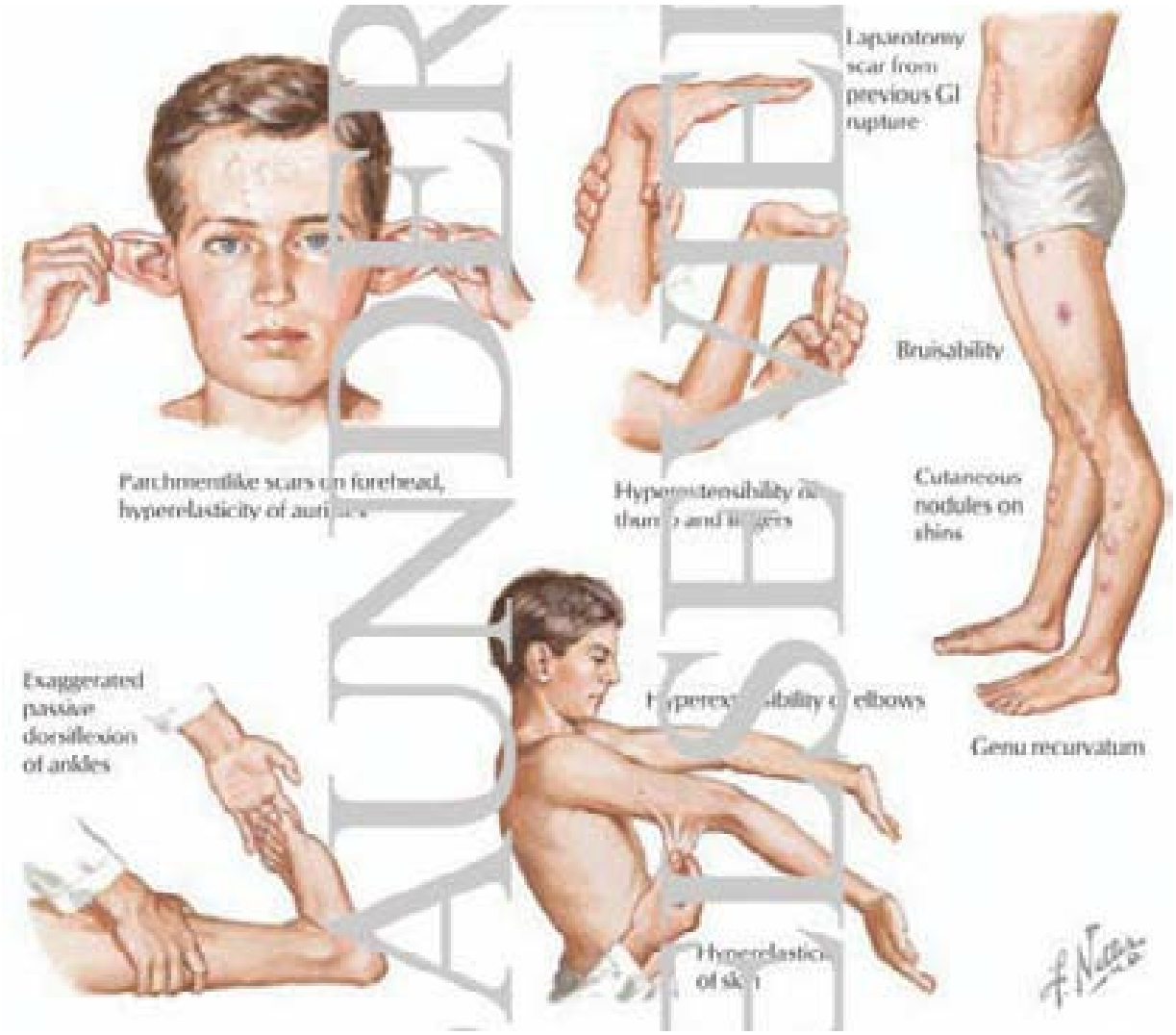
- Hereditary motor and sensory neuropathy.
- Begin between childhood and young adulthood.
- Muscle weakness, atrophy, loss of sensation and diminished reflexes.
- Affecting first the legs, progressively spread to affect different parts of body, including diaphragm and vocal cord.
- Foot drop, abnormal gait, skeletal deformities.
- Episodic painful muscular contractions.

Autosomal Dominant

EHLERS DANLOS SYNDROME

Chromosome 2, Gene COL 5 A 2, Location 2 q 32.2

Named after, Edvard Ehler, Dermatologist (Denmark) and Henry Danlos, physician (France), in 1908.



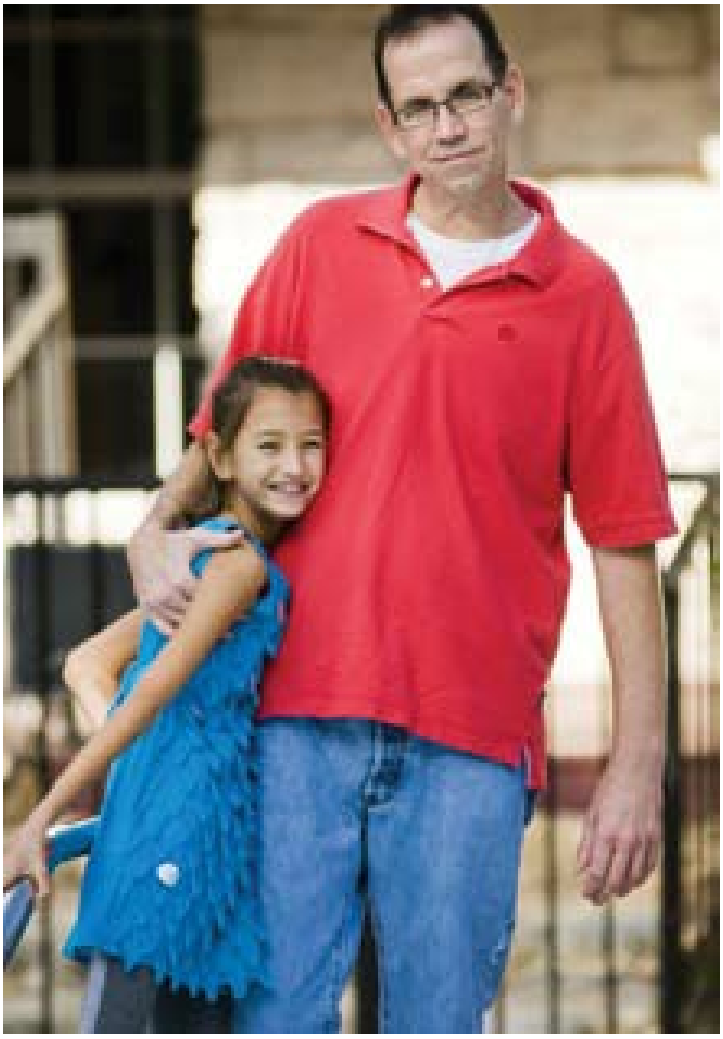
Incidence: 1 / 5000 Births.

- Connective tissue disorder, elasticity of skin.
- Hyperflexability of joints, hypotonia, skeletal deformities.
- Congenital heart defect (aortic aneurysm).
- Blue sclera, retinal detachment.
- High arched palate.

MARFAN SYNDROME

Chromosome 15 Gene FBN 1, Location 15 Q 21.1

Described by, Dr.Bernard Marfan, French Paediatrician,1896



Incidence: 1 / 5000 Births .

- Connective tissue disorder.
- Tall and slender, arm span exceeds body height.
- Skeletal deformities; either scoliosis or kyphosis.
- Sunken chest, pectus excavatum, or pectus carinatum.
- Arachnodactyly.
- Dislocated lens in one or both eyes.
- Congenital defect in heart (Aortic dilatation).

BECKWITH-WIEDEMANN SYNDROME

Chromosome 11p15

Described by Drs. Beckwith and Wiedemann in 1969.

Incidence: 1/14.000 births.

- Paediatric overgrowth syndrome.
- Large for gestational age.
- Microcephaly.
- Macroglossia.
- Enlargement of some organs and tissues.
- Abdominal wall defect (omphalocele, umbilical hernia).
- Creases in ear lobes and may be low set ears.
- Cryptorchidism.
- Poor feeding.
- Hypoglycaemia.
- Seizures.
- ↑ Risk of childhood cancer.

ALAGILLE SYNDROME

Chromosome 20, Gene JAG 1, Location 20 p 12

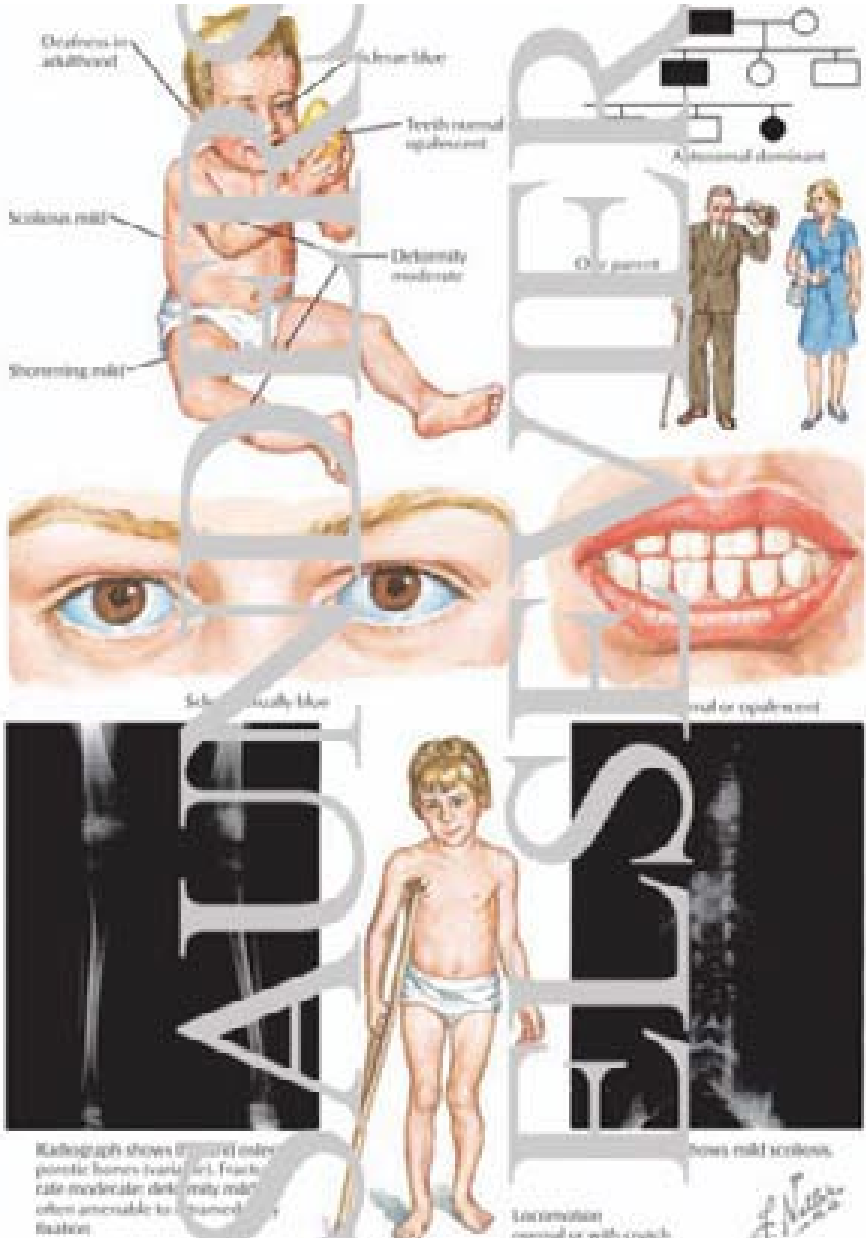
Described by Dr. Alagille et al, France in 1975

Incidence : 1 / 10.000 Births.

- Abnormalities in the bile ducts of liver.
- Cholestasis, jaundice.
- Deep-set eyes, and prominent forehead.
- Deposition of cholesterol in the skin (xanthomas).
- Congenital heart defect (pulmonary stenosis).
- Renal anomalies.

OSTEOGENESIS IMPERFECTA

Chromosome 3, Gene FPRE1, Location 3 p 22.3



Incidence: 1/20.000 Births.

- Extremely fragile bones.
- Skeletal deformities.
- Pathological fracture of bones.
- Deafness, and Blue Sclera.

ACHONDROPLASIA

Chromosome 4, Gene FGFR 3, Location 4 p 16.3

Incidence: 1 / 25000 Births.

- The problem in converting cartilage to bones, particularly in long bone of the arms and legs.
- Short - limbed dwarfism.
- Average adult height about 4 feet (120 cm).
- Normal sized torso, large head with prominent forehead.
- Redundant skin folds in arms and legs.
- Hypotonia.

CROUZON SYNDROME

Chromosome 10, Gene FGFR 2, Location 10 q 26.13

Named after, Dr. Octave Crouzon a French Physician in 1912.

Crouzon syndrome

Incidence: 1 / 25000 Births.

- Premature obliteration and ossification of one or more of the cranial sutures.
- Most often coronal and sagittal.
- Exophthalmos.
- Hypertelorism.
- Strabismus (eyes that do not point in the same direction).
- Dental deformities.
- Mental Retardation.

WAARDENBURG SYNDROME

Chromosome 2, Gene PAX 3, Location 2 q 36.1

Named after Dutch ophthalmologist Dr. Petrus Johannes Waardenburg, 1951

Waardenburg syndrome

Incidence: 1 / 42000 people.

- Hypopigmentation of skin and hair or distinctive hair colouring (such as patch of white hair or hair prematurely turns gray).
- Medial eyebrow flare (synophrys).
- Two differently coloured eyes or brilliant blue iris.
- Hearing loss with varying degrees affect one or both ears.

CLEIDO CRANIAL DYSPLASIA

Chromosome 6, Gene RUNX 2, Location 6 p 21.1

In Greek; Cleido, Collarbone. Cranial, Head, Dysplasia, Abnormal form.

Cleido Cranial Dysplasia

Incidence: 1 / 200.000 Births .

- Affects the development of bones and teeth.
- Shorter than other members of their family.
- Incomplete or absent clavicles.
- Deformities of vertebral column.
- Osteopenia, may develop osteoporosis.
- Under mineralization of skull bones.
- Delayed closure of fontanels may remain open into adult age.
- Boosing of head, high arched palate and defective tooth.

APERT SYNDROME

Chromosome 10, Gene FGFR 2, Location 10 q 26.13

Recorded by, Dr. Eugan Apert, France, In 1906.

Apert Syndrome

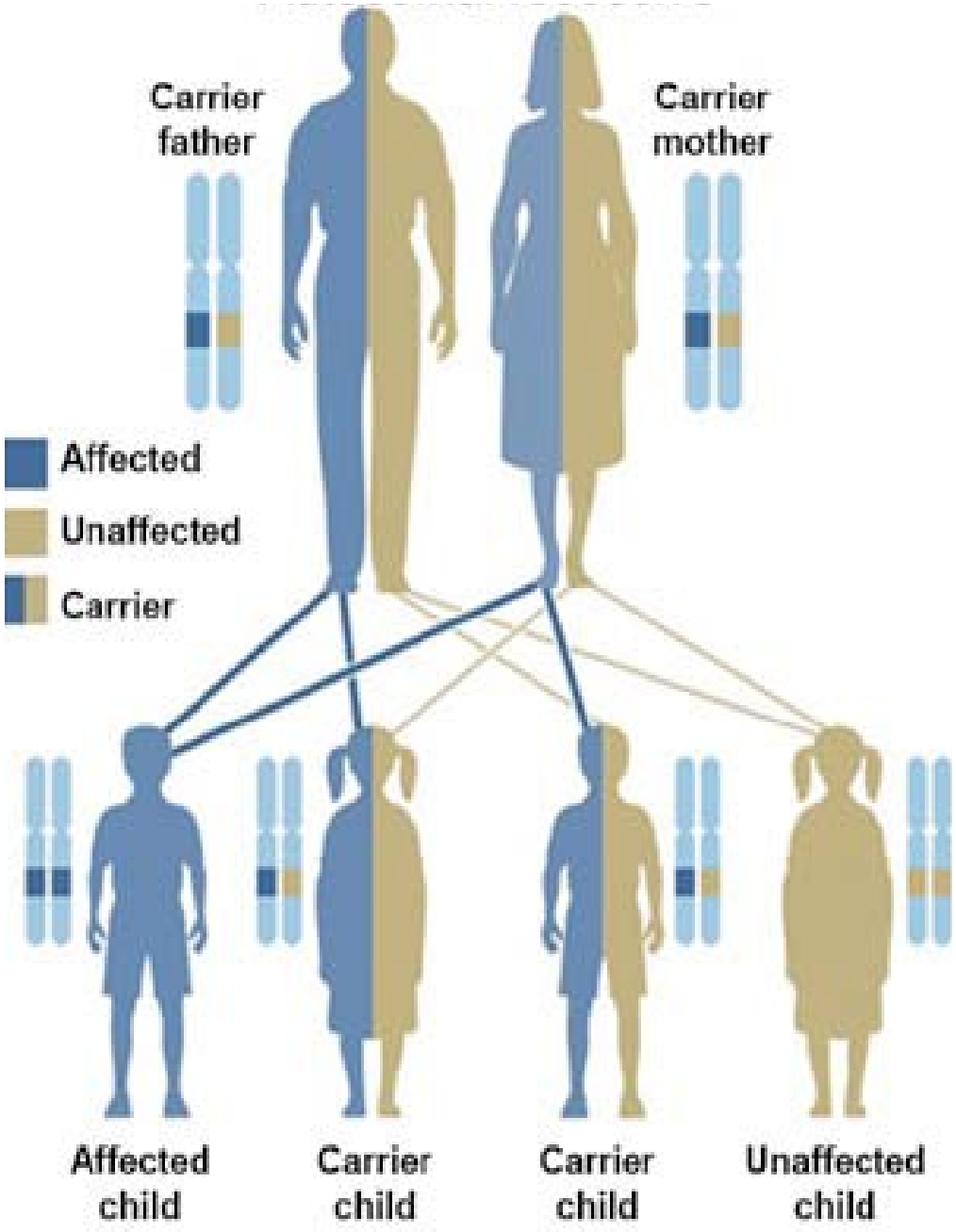
Defrmed high arched palate and dental deformities.

Incidence: 1 / 200.000 Births.

- Premature closure of one or more of the cranial sutures.
- Abnormal facial features.
- Mental retardation.
- Bossing of head.
- Exophthalmos,and hypertelorism.
- Depressed nasal bridge.
- Deformed high arched palate, and dental deformities.
- Syndactyly.

AUTOSOMAL RECESSIVE

- Both parents are carrier (heterozygous) for the mutant gene.
- Both parents are asymptomatic.
- The Chance of inheriting the disorder to their siblings is 25%

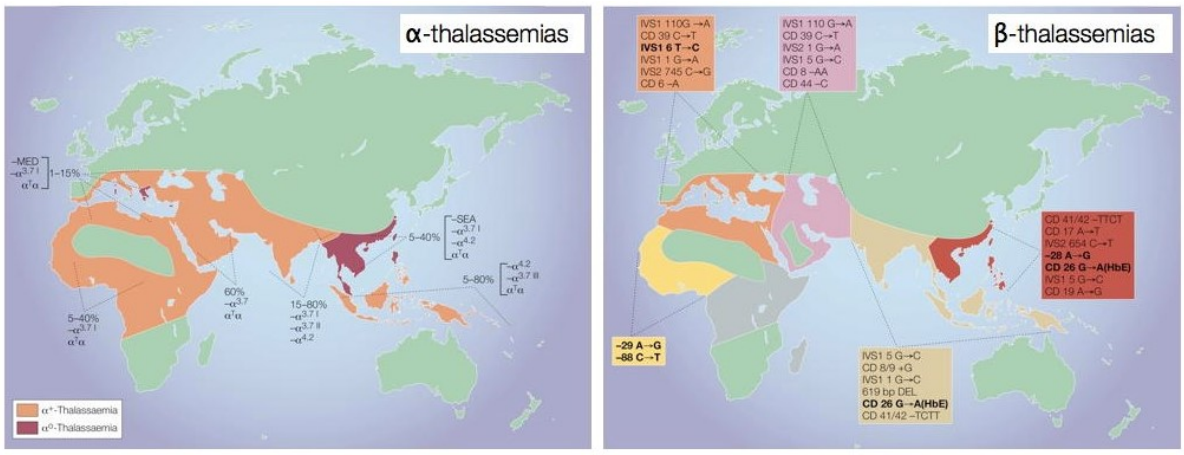


Autosomal Recessive

BETA THALASSEMIA

Chromosome 11, Gene HBB,Location 11 P 15.5

In Greek Thalassic (Sea) and Emia (Blood), described in 1932.



Young girl and thalassaemic features

Defective production in B chain of haemoglobin.

Incidence

- Prevalent in Mediterranean people.
- Highest incidence in Cyprus and Maldives where the carrier rate is 18 % of population.

Clinical Picture

- Pallor.
- Symptoms started by age 6 months.

- Mongoloid features, prominent check bone (expansion of marr-ow cavity of bones of skull and face, protrusion upper jaw from extramedullary erythropoiesis).
- Growth retardation.
- Deposition of iron anywhere in the body (sidrosis).
- Hepatosplenomegaly.
- Poor prognosis and children die before adolescency.

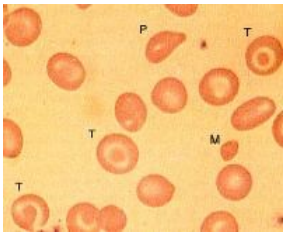
Diagnosis

✓ Hb electrophoresis: ↑ Hb F 80-90% by age 3 months+ ↓ Hb A.
(normally Hb F < 10% by age 3 months, and Hb A represent 90%)

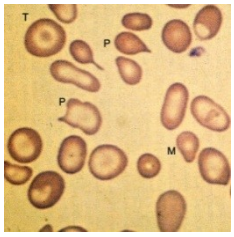
✓ CBC: severe microcytic hypochromic anaemia, target cells, retic-ulocytosis, leucopenia, and thrombocytopenia.

✓ ↑ Serum iron.

✓ Carrier state: Hb A_2 > 3.5 %, Hb F is zero, and HbA is normal.



Peripheral blood smear in Beta-Zero Thalassemia Minor showing Microcytes (M), Target cells (T), and Poikilocytosis(P)



Peripheral blood smear in Beta-Zero Thalassemia Major showing more Anisop-oikilocytosis(P), Target cells (T), marked microcytosis(M), prominent hypochromia.

Management

➢ keep Hb > 10 gm/dL.

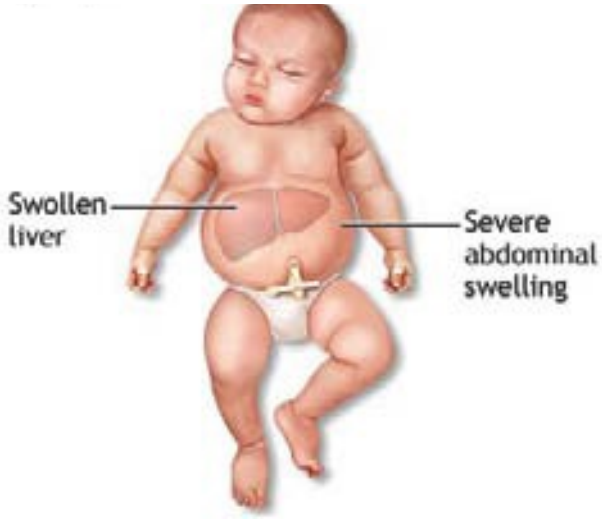
➢ Packed red cells transfusion, nearly will need 2 units / month.
(Normal Hb-patient Hb) X B.Wt X 3.5 (or 10-15 ml/Kg).

One unit packed cells ↑ Hb level 1 gm/dL.

- Iron chelation: Desferoxamine ampule 500 mg, 20 mg/kg intrave-nous over 5 hours, diluted with glucose 5 % 50 ml or intramuscular daily for 5 days/week.
- Vitamin C tablet or effervescent daily 1 X 1.
- Folic acid 5 mg tablet / day.
- Splenectomy: massive splenomegaly interfering with breathing , post splenectomy immunization by Pneumovax and Meningovax (usually required by age of 8 years).
- Genetic induction of Hb A by Erythropoietin (Eprax) ampule 4000 U, twice weekly for one year.
- Bone marrow transplantation, curative, highly specialized centres.
- Premarriage counselling and public awareness.

ALPHA THALASSEMIA

Chromosome 16, Genes HBA1and HB A 2, Location 16 p 13 - 3.



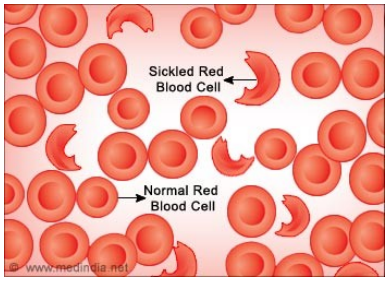
Homozygous Alpha Thalassemia
Hydrops Fetalis (HB Bart's).

- Defective production of alpha chain of haemoglobin.
- Human cells contain 2 copies of Haemoglobin A_1 and 2 copies of Haemoglobin A_2, by means that the disease is under control of 4 genes.
- Absence of the 4 genes (Homozygous Alpha Thalassemia) result in production of Haemoglobin Bart's (Hydrops Fetalis) which is incompatible with live.
- Absence of the 3 genes (Heterozygous Alpha Thalassemia) result in production of Haemoglobin H.
- Absence of the 2 genes (Alpha Thalassemia trait) presented with microcytic hyp-ochromic anemia.
- Absence of 1 gene (Alpha Thalassemia Silent) is asymptomatic.

SICKLE CELL ANAEMIA

Chromosome 1, Gene HBB, Location 11 p 15.4

Discovered by, Cardiologist Dr .James B. Herik, USA, in 1904.



- θ It is abnormality in the shape of RBCs
- θ Usually started by age 6 months with the replacement of HbF by Hb SS or Hb SA.

(Normally at birth, about 80 % is HbF & 20 % is HbA & by age 3 months, about 90 % is HbA & 10 % is HbF).

- θ In sickle cell disease haemoglobin is either:
  - ≈ (Hb SS) 80 - 90% - sickle cell anaemia.
  - ≈ (Hb SA) 50% S & 50% A - sickle cell trait.

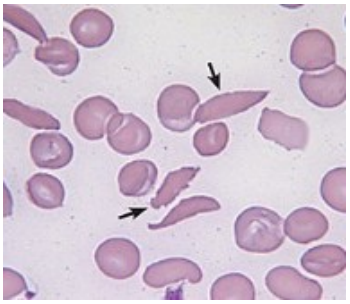
Incidence: 75 % of cases occur in Africa, where carrier rate about 10-40%

Clinical picture

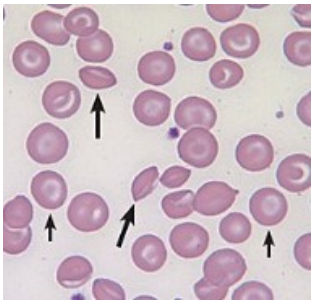
- Commonest presentation is Vasoocclusive crises affecting hands and foot (Dactylitis) as painful, symmetric swelling of hands and feet or recurrent painful episodes of Abdominal Pain from affection of any internal organ, crises occur nearly on daily basis, may affect kidney, spleen, may cause Priapism, or acute chest pain, may affect brain (cerebrovascular occlusion- stroke - or affect retina - Angioid Streaks.
- The patient is very susceptible to infection, especially malaria in the endemic areas, so given antimalarial drugs in daily basis in such areas.

Diagnosis

- ✓ Hb electrophoresis: detect presence of Hb SS, or AS.
- ✓ CBC: severe normocytic normochromic anaemia(Hb 5-7gm/dl), reticulocytosis, Howell jolly bodies which may indicate hyposplinism, anisocytosis, poikelocytosis ,neutrophilia,thrombocytosis.
- ✓ ESR: ↓ as sickle cells fail to form rouleaux.
- ✓ Sonar Abdomen: may show evidence of internal organ damage.
- ✓ CT scan Brain: may show multiple tinny infarcts.
- ✓ Liver & Renal function tests: evidences of damage.
- ✓ Fundus examination: may show Angioid Streaks.



Peripheral blood smear of a patient with Hb SS disease, Arrow indicates classic sickle cell.



Peripheral blood smear of a patient with Hb SC, Short arrow indicates Target cells, Long arrows indicate Atypical sickle cells.

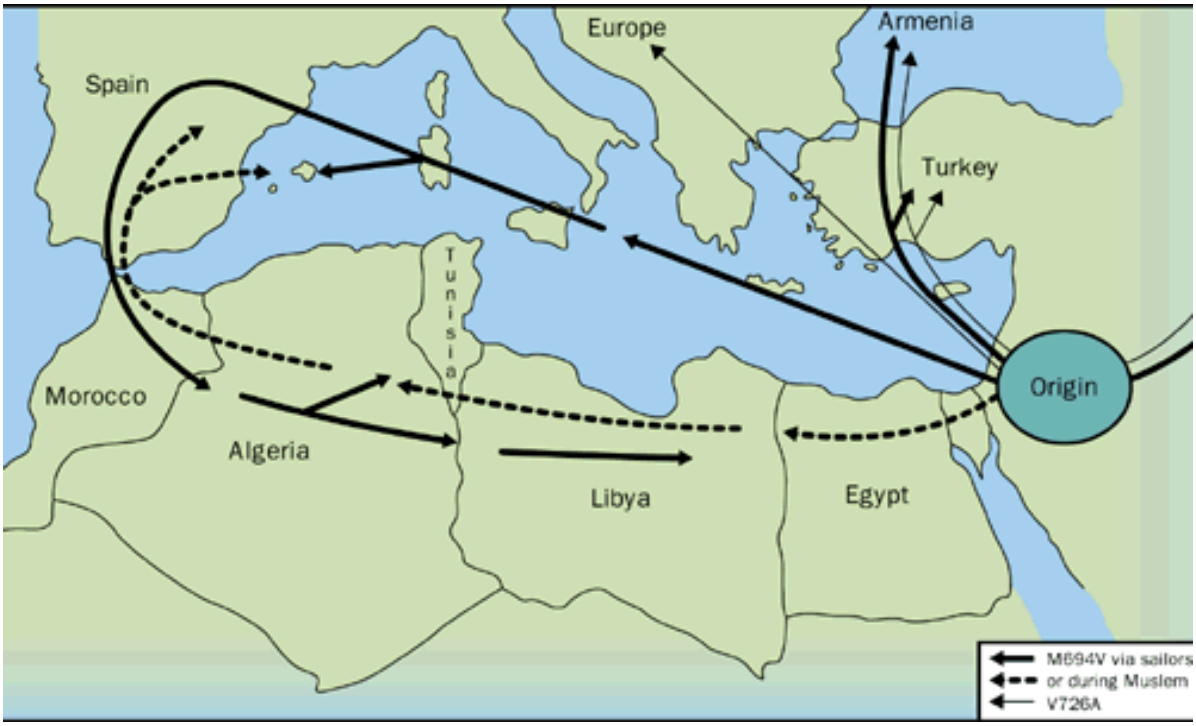
Management

- Avoidance precipitating factors as fever, dehydration, hypoxia, acidosis, or infection.
- Intravenous fluid: overhydration using 150 % of the maintenance daily require.
- Analgesics: Morphia, Codeine, Aspirin for those > 5 yrs (to avoid Reye`s syndrome), Paracetamol drops 100 mg/dropper, syrup 250 mg, suppository 120 mg, maximum total daily dose is 1200 mg, Marcofen paed. supp. 100 mg 1 X 2 for infant > 6 months.

- Prophylactic antibiotics.
- Vitamin C and Folic acid daily requirement.
- Vaccination: the routine vaccination + pneumococcal vaccine.
- Blood transfusion: if Hb < 5 gm, using whole blood transfusion (Normal Hct – Patient Hct) ÷ Donner Hct) X BLood Volume. (Blood Volume = B.Wt. X 80 ml).
- In endemic areas of malaria, prophylactic antimalarial drug is needed in daily basis
- Haematopoietic cell transplant: curative.

FAMILIAL MEDITERRANEAN FEVER

Chromosome 16, Gene FMF, Location 16 p 13.3



Incidence

1/ 500 Armenian and Sephardi Jews.

1/2600 in Arabs.

- First episode usually occurs in childhood or teenage years.
- Painful episodes last for 12-72 hours in the form of abdominal pain, joint pain, chest pain.
- Fever.
- Skin lesions.
- No specific diagnostic test except chromosomal study.
- Colchicine reduces the inflammation.

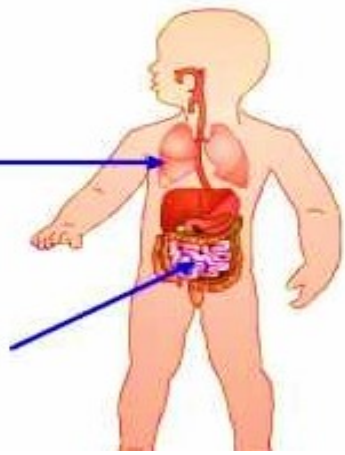
CYSTIC FIBROSIS

Chromosome 7, Gene CFTR, Location 7 q 31.2 (1930s)

Incidence: the most common fatal Autosomal recessive disease in Europe, seen in 1/ 3000 Births, in U.S.A. and Europe.

- Abnormal transportation of chloride and sodium across epit-helium leading to thick viscous secretions.
- Salty tasting of skin.
- Recurrent chest infection.
- Meconium ileus, intestinal obstruction.
- Chronic diarrhoea.
- Congenital absence of vas deferens and infertility.
- Nasal polyposis.
- Rectal prolapse.
- Cholelithiasis.
- Pancreatitis.
- Liver Cirrhosis

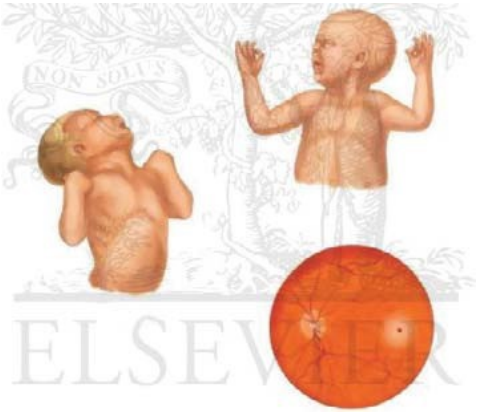
Mucus in patients with cystic fibrosis is very thick and collects in the intestines and lungs. The result is malnutrition, poor growth, numerous respiratory infections, breathing difficulties, and eventually, permanent lung damage. Lung disease is usually the cause of death in most patients.



TAY SACHS DISEASE

Chromosome 15, Gene HEXA, Location 15 .q 23

Named after Dr. Warner Tay, British ophthalmologist 1881 and Dr. Bernard Sachs, American neurologist, in 1887.



Tay Sachs Disease

Incidence: 1/3500 in Jewish & 1/320.000 in general population.

- Metabolic disorder.
- Deficiency of enzyme B-Hexosaminidase A, results in accumulation of fatty acid derivative (ganglioside) in neurones.
- Infantile type is the commonest and severest form, tend to get worse very quickly and child usually dies by age 4 - 5 years.
- Delayed milestones.
- Paralysis.
- Convulsions.
- Blindness, Cherry Red Spots in Eyes.
- Deafness.
- Dementia.
- Psychosis.

PHENYLKETONURIA

Chromosome 12, Gene PAH, Location 12 q 23.2

Discovered by Norwegian physician Dr. Ivan Folling, in 1934.

Symptoms can minimize by adherence to a strict phenylalanine free diet

Incidence: 1/10.000 Births.

- Inborn error of metabolism.
- Deficiency of enzyme phenylalanine hydroxylase.
- Delayed milestones.
- Vomiting.
- Frequent Diarrhoea.
- Musty odour of skin, hair and urine.
- Skin problems, and sensitivity to light.
- Irritability.
- Brain damage.

MAPLE SYRUP URINE

Chromosome 19, Gene BCKDHA, Location 19 q 13.2

Described by American paediatrician Dr. Menkes et. Al, in 1954

Incidence 1/180.000 Births.

- Disorder of branched chain amino acids metabolism; Leucine, Isoleucine and Valine.
- Accumulation of these 3 amino acids and their corresponding keto acids leads to encephalopathy and progressive neurodeg-eneration
- Distinctive sweet odour of urine, smell is also present and someti-mes stronger in ear wax.
- Lethargy.
- Seizures.
- Brain Damage.
- Coma.

Investigations

- ✓ Urine Amino Acid Test
  - Valine: normal level in children: 17 to 37, adults: 19 to 74
  - Leucine: normal level in children: 9 to 23, adults: 20 to 77
  - Isoleucine: normal level in children: 3 to 15, adults: 4 to 23
- ✓ Plasma Amino Acid Test for valine, leucie, isoleucine.
- ✓ Chromatography: baby should not eat for 4 hours before.

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Chromosome 6, Gene CYP 21 A 2, Location 6 p 21.33, described 1960.

Each adrenal gland has two parts:

*Adrenal Medulla (inner area)

Secretes catecholamines which mediate stress response (help prepare a person for emergencies).

- Norepinephrine.
- Epinephrine.
- Dopamine.

*Adrenal Cortex (outer area, encloses Adrenal Medulla)

Secretes steroid hormones.

- *Mineralocorticoids*: are essential to maintain sodium and fluid balance.
- *Glucocorticoids*: exert a widespread effect on metabolism of carbohydrates and proteins.
- Sex hormones (secondary source).

Zona glomerulosa,produces predominantly mineralocorticoids.

Zona fasciculata, produces predominantly glucocorticoids.

Zona reticularies, produces predominantly androgens.

- CAH is familial disorder of adrenal steroid biosynthesis.
- The defect is expressed as adrenal enzyme deficiency.
- 5 major Enzyme deficiency are clinically important:
  - 21 Hydroxylase.
  - 11- b-Hydroxylase.
  - 17-a-Hydroxylase.
  - 3-b-Hsteroid hydrogenese.

- 20, 22 Desmolase deficiency.

- The enzyme deficiency causes reduction in end-products, acc-umulation of hormone precursors and ↑ ACTH.
- The clinical picture reflects the effects of inadequate producti-on of cortisol and aldosterone and the ↑ production of androgens and steroid metabolites.

21 Hydroxylase deficiency

Most common type, accounts > 80 % of cases.

Incidence: 1: 5000 to 1: 15000 live births.

- Gene is located on the short arm chromosome 6 near the C 4 locus in close ass-ociation with HLA genes.
- Heterozygous carriers can detected by ACTH stimulation test.
- It is characterised by ↓ production of cortisol and aldosterone and ↑ production of progesterone; 17-OH-progesterone, and sex steroids.
- The urinary steroid metabolites (17-ketosteroids and pregnanetriol) ↑ above normal levels.
- ↓ secretion of aldosterone results in salt loss with hyponatremia and hyperkala-emia; plasma renin activity is therefore ↑.
- In partial enzyme deficiencies, the aldosterone deficiency is not expressed, patient remain normonatremic and normokalemic.
- The ↑ androgens causes virilisation of girls, or ambiguous genit-alia and dark scrotum in boys.
- There are 2 forms, classic early virilization type with or without salt-losing crisis & non-classic type with late-onset virilization.
- Male babies with non salt-losing (non-classic type) remains asymptomatic till

childhood when showing sexual precocity signs.

- Because members of the same family may have classic, or non-classic & asympt-omatic forms, the disorder may be due to allelic variations of the same enzyme.

Clinical Picture: commonly presented with:

- Ambiguous genitalia, labial fusion, clitromegaly, or penile, testi-cular enlargement and will developed muscles in boys, early ap-pearance of pubic, armpit hair, hyperpigmentation of genitalia.
- Advanced bone age.
- Poor feeding.
- Diarrhoea.
- Dehydration.
- Electrolyte disturbances.
- Arrhythmia.

↑ androgen production results in Ambiguous genitala in newborn Girl-classic form.

Women with excess hair growth. - non classic form.

Investigations

- Chromosomal studies: a Karyotype is essential in the evaluation of the infant with ambiguous genitalia in order to establish the chromosomal sex.
- Neonatal screening: done by measuring 17-OH-progesterone from heel blood sam-ples collected on filter paper. This approach allow early identification of newborns with CAH and prevent salt wasting crisis in boys who are unrecognized at birth. It also identifies the completely virilised girls with ambiguous genitalia who may be

mistaken for boys with cryptorchidism.

- Prenatal diagnosis of adrenal hyperplasia is possible through biochemical and genetic tests.
- ↑ Adrenocorticotrophic hormone (ACTH).
- ↑ 17-OH- progesterone, or 11 beta hydroxyldeoxy progesterone in blood and urine (may be ↑ 20 times).
- Advanced bone age (from excess androgen).

Management

- ✓ Replacement therapy: (4S) Steroids, Sugar, Salt, Sodium bicarbonate for metabolic acidosis.
- ✓ Correction of dehydration, acidosis, and electrolyte imbalances.
- ✓ Prednisolone(5 time potent than hydrocortisone), 1 mg/Kg /day
- ✓ Florinef (9-alpha fludrocortisone) 0.1 mg tablet as one tablet daily in case of Aldosterone deficiency.

11- B - Hdroxylase Deficiency

- ♦ Accounts for 5-10 % of cases of CAH.
- ♦ Gene is located on the long arm of chromosome 8.
- ♦ Characterized by ↓ plasma renin activity and ↑ high serum 11-deoxycorticosterone and 11-deoxycortisol concentrations with ↑ of its urinary metabolities tetrahydro (compound-S)
- ♦ Because of the strong mineralocorticoid activity of deoxycorticosterone, the condition is characterized by salt retention, hype-rtension, and hypokalemic alkalosis.
- ♦ ↑ Plasma androgens may cause virilisation of female fetus.

17- α – Hydroxylase deficiency

- ☼ Genetic defect is on chromosome 10.
- ☼ Presents with similar features of those of 11-Hydroxylase deficiency except that androgens are low, so no virilisation in girls and genitalia is ambiguous in boys.

3- B- Hydroxysteroid dehydrogenase deficiency

- ω This is a very rare disorder that results in accumulation of DHEA, which is converted to testosterone in peripheral tissues.
- ω It can cause virilisation of female fetus and leads to ambiguous genitalia in the newborn.

WERDNIG HOFFMAN DISEASE

Chromosome 5, Gene SMN 1, Location 5 q 13.2

Described by Dr.Guido Werdnig, Australian neurologist and Dr.Jehann Hoffman German neurologist in 1891.

Infantile type, Werdnig Hoffman Disease in 6-month-old infant.

Incidence: 1/10.000 Births.

- The most common genetic cause of infant death.
- Degenerative disease of nerve cells of lower brain steam and anterior horn cells of the spinal cord.
- The infantile type is the severest form, represent 80% of cases.
- Muscle weakness.
- Floppy infant, Frog leg position.
- Dysphagia.
- Poor feeding.
- Accumulation of secretions in lungs, and respiratory distress.
- Delayed milestones.
- Areflexia.
- Skeletal deformities.
- Fasciculations (twitching of the tongue).
- Baby usually dies by the age of 20 months.

GASTROSCHISIS

Chromosome 3 , Location 3 Q 27.3

Gastroschisis

Incidence 1/ 10.000 Births.

- Anterior abdominal wall defect.
- Usually less than 4 cm. to the right side of the umbilicus.
- Protrusion of abdominal content.
- No covering sac.

Cover with sterile gauze soaked in saline, and transfer to surgery.

ALBINISM

Chromosome 11 , Gene TYR , Location 11q14.3

African child with Albinism

Incidence 1/17000/ Births.

- Defect in melanin production that results from absence or def-ect of tyrosinase (a copper containing enzyme) involved in production of melanin.
- Little or no colour (pigment) in the skin, hair, and eyes.
- Photophobia.
- Strabismus.
- Nystgmus.
- Functional blindness.

SMITH-LEMLI-OPITZ SYNDROME

Chromosome 11, Gene DHCR7, Location 11 q 13.4

Described by Belgian Pediatricians Smith Lemli, Luc Lemli and John Optiz, 1964

Smith-Lemli-Opitz Syndrome

Incidence 1/20.000/ Births (Caucasian).

- Delayed milestones.
- Mental retardation.
- Microcephaly.
- Cleft palate.
- Defective dentation.
- Syndactyly and Polydactyly.
- Hypospadias.
- Cryptorchidism.

HURLER SYNDROME

Chromosome 4, Gene IDUA, Location 4 p 16.3

Named after, Australian Paediatrician Gertrud Hurler in 1919.

Hurler Syndrome

- Incidences 1 /100.000 Births .
- Inborn error of metabolism (Mucopolysaccaroidosis type 1).
- Deficiency of Alpha-1-Iduronidase enzyme.
- Coarse facial features, low flat nasal root, macroglossia, widely spaced teeth.
- Mental Retardation.
- Delayed milestones.
- Short stature.
- Clouding of cornea.
- Hepatosplenomegaly.
- Progressive deterioration with death occurring by age of 10 yr.

BARDET BIEDL SYNDROME

Chromosome 11 , Gene BBS1, Location 11q13.2

Named after Dr. Bardet G.(France) in 1920 and Dr. Biedl A.(Dutch)in 1922

Bardet Biedl Syndrome

Incidence 1 / 150.000 Births in USA and Europe.

1 / 14.000 Births in Middle East.

- Mental Retardation.
- Obesity.
- Poldactyly and Syndactyly.
- Hypogenitalism.
- Retinitis pigmentosa.
- Visual impairment.

COHEN SYNDROME

Chromosome 8, Gene COH 1, Location 8 q 22.2

Named after American geneticist Michael Cohen in 1973

Cohen Syndrome

Incidence: very rare < 1 / 200.000 people.

- Diagnosis is generally raised at school age.
- Mental Retardation.
- Square head, short neck, and full cheeks.
- Microphthalmia, epicanthus fold, downward slanting of eyes, and long eyelashes.
- Chorioretinal dystrophy, and visual impairment.
- Upper lip is thin and does not cover the front teeth (giving an open mouth expression) with prominent upper central incisors.
- Thick hair.
- Mild cutaneous syndactyly.
- Obesity in late childhood or adolescency.

NIEMANN PICK SYNDROME

Chromosome 11, Gene SMPD 1, Location 11 p 15.4

Named after Dr. Albert Nieman and Dr. Ludwig Pick, in 1920.

Niemann Pick syndrome

Incidence: 1 / 250.000 whole world.

1 / 40.000 Ashkenazi Jews.

- Lipid storage disease.
- Harmful accumulation of lipids in liver, spleen, lungs, bone mar-row and brain (Sphingolipidosis).
- Failure to thrive.
- Prolonged jaundice.
- Hepatosplenomegaly.
- Progressive deterioration of central nervous system.
- Seizures.
- Dysphagia, Dysarthria, Dystonia, Dementia.
- Ophthalmoplegia.

COCKAYNE SYNDROME

Chromosome 5, Gene ERCC 8, Location 5 q 12.1

Named after British Dr. Alfred Cockayne in 1936

5 years Girl with Cockayne Syndrome

Incidence: 1 / 250.000 Births

- Defect in DNA repair mechanism.
- Affect any or all organs of the body.
- Progressive disease.
- Typically become apparent after age 1 year.
- Delayed milestones.
- Senile appearance.
- Sensitivity to sunlight's, and sun exposure can cause sunburn.
- Deafness.
- Pigmentary retinopathy and eye abnormalities.

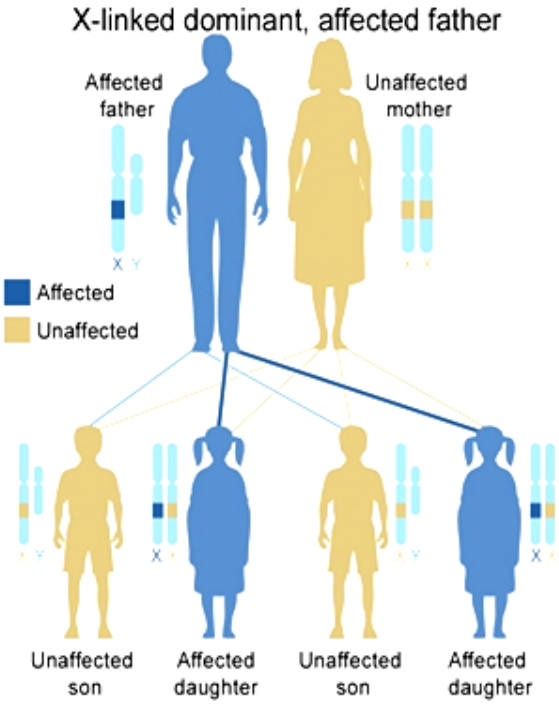
X - LINKED DISORDERS

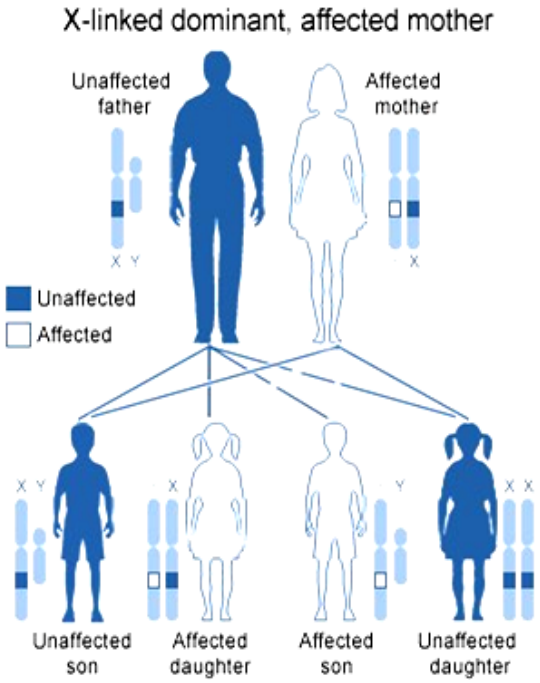
X - LINKED DOMINANT

Characteristic of X- Linked inheritance is that fathers cannot pass X - linked triats to their sons. (No Male - To - Male Transmission).

If Father affected: All of his daughters will be affected & none of his sons will be affected.

If Mother affected: 50% chance of sibling to be affected regardless of sex.





FRAGILE X SYNDROME

X chromosome, Gene FMR 1, Location X q 27.3

Fragile X Syndrome

Incidence 1 / 5000 children.

- The most common form of inherited mental retardation.
- Baby often large for gestational age, and head circumference more than 90th centile.
- Long face.
- Prominent and elongated ears.
- Macroorchaidism.

RETT SYNDROME

X-Chromosome, Gene MECP 2, Location X q 28

Described by, Andreas Rett, Austrian, paediatrician in 1966.

Rett Syndrome.

Incidence: 1 /10.000 Births.

- ☺ Disorder of the central nervous system.
- ☺ Affect especially areas of expression.
- ☺ Affect language: severe language development problems.
- ☺ Affect hand use, Apraxia, inability to perform motor function, and hand motion abnormalities.
- ☺ Delayed milestones start to appear by age 6-18 months.
- ☺ Autistic like behaviour, diminished eye contact and loss of nor-mal sleep pattern.
- ☺ Excessive salivation and drooling.
- ☺ Floppy arms and legs, shaky, unsteady stiff gait or toe walking.
- ☺ Breathing problems, which get worse with stress but normal during sleep.

CORNELIA DE LANGE SYNDROME

X chromosome , Gene DXS 423 E , Location X p 11.22

Named after Cornelia De Lange, Dutch Paediatrician in 1933 .

Cornelia De Lange syndrome

Incidence 1 / 10.000 - 100.000 live births.

- Delayed milestones.
- Mental retardation.
- Hirsutism with low anterior and posterior hairlines.
- Arched eyebrows, and long eyelashes.
- Small upturned nose.
- Crescent shaped mouth, and small widely spaced teeth.
- Low set ears.
- Limb deformities.

HYPOPHOSPHATEMIC RICKETS (Vitamin D resistant Rickets)

X Chromosome, Gene, PHEX , Location X p 22.11

Rickets

Incidence 1 / 20.000 Births.

- ✓ Delayed physical milestones: teething, walking etc.
- ✓ Delayed closure of fontanels, craniotabes, bossing of head.
- ✓ Broadening of wrist and ankles.
- ✓ Rachitic rosary at costochondrial junction.
- ✓ Green stick fracture of bones.
- ✓ Skeletal deformities, bowing of legs.
- ✓ ↓ Serum Phosphors, ↑ Serum Alkaline Phosphatase.
- ✓ Normal serum calcium, 1- 25 dihydroxyvitamin D, and parathy-roid hormone (PTH).

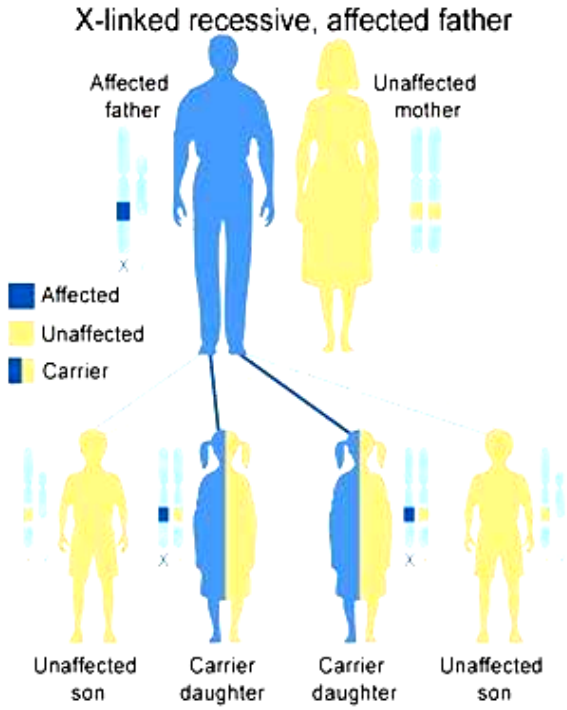
Give oral phosphate and calcitriol.

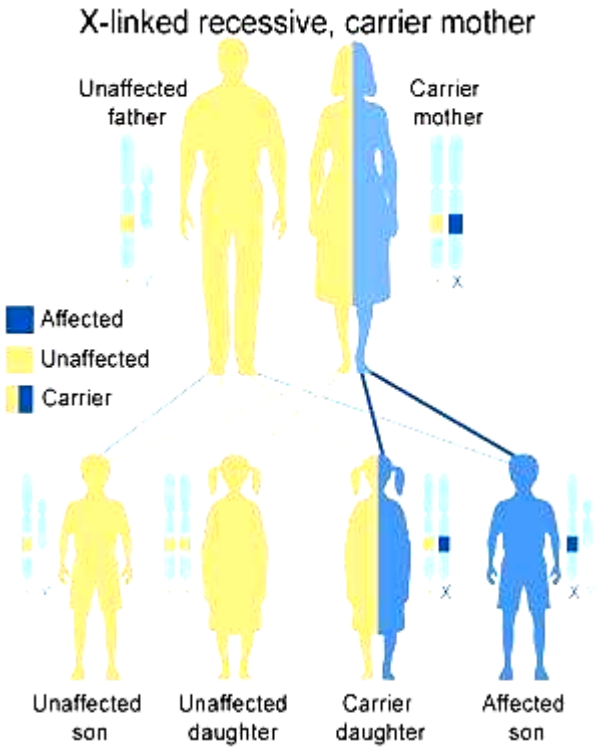
X LINKED RECESSIVE

A characteristic of X-Linked inheritance is that fathers cannot pass X- linked triats to their sons (No Male- to -Male Transmission).

If Father affected: none of his sons will affected but all daughters are carriers.

If Mother carrier: there will be 50 % chance for sons to be affected & 50 % chance for daughter to be a carrier.





COLOR BLINDNESS

X - Chromosome Gene, OFN1LW, Location Xq28

Described by, English Chemist, John Dalton in 1798

Incidence: 5 % in males & 0.5 % in females.

- Inability or ↓ ability to see colour, or perceive color differences under normal lighting conditions.
- People usually have 3 types of cone cells in the eye, each type senses either red, green or blue light (3 basic colors), and most of cone cells are found in macula, which is the central part of Retina.

Normal color vision

Normal color vision

GREEN COLOR BLIND (Deuteranopia)

The commonest 95%

No Green

BLUE - COLOUR BLIND (Tritanopia)

No Blue

RED COLOR BLIND (Protanopia)

No Red

TOTAL COLOR BLINDNESS (Monochromacy).

All colos are lost

Only as if it were on a black and white television as 2-3 cone pigments are missing.

GLUCOSE 6 PHOSPHATE DEHYDROGENASE DEFICIENCY

X Chromosome, Gene G6PD, Location X q 28

Incidence

Common in Negros, and Middle East.

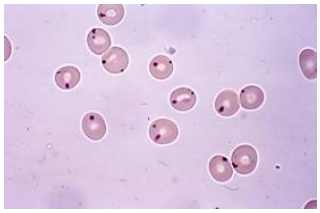
Occur in 11-13% of African Americans.

Estimated 400 million people worldwide carry the gene.

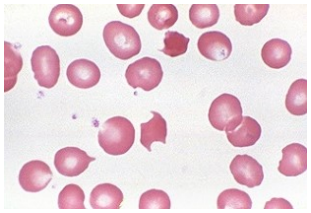
- Result from break down of red blood cells, which can be triggered by infections, severe stress, and certain foods.
- Episodic hemolysis from **fava beans**, oxidant drugs (especially primaquine, sulpha drugs, amiodarone, antimalarial, nitrofurantoin, antihistaminics, anti - tuberculous, aspirin).
- Significant cause of mild to severe jaundice in newborns.
- Presentation
  - Anaemia.
  - Fatigue.
  - Tachycardia.
  - Shortness of breath.
  - Dark urine.
  - Splenomegaly.

Diagnosis

- CBC and Blood Smear



B. Smear- G6PD, showing Heinz Bodies (denatured hemoglobin).



B. Smear- G6PD, showing Bite cells.
Prussian blue staining (detects hemosiderin)

- G6PD levels are usually paradoxically normal during haemolytic episode.

  Notes: patients are less susceptible to malaria.

Differential Diagnosis

Sickle cell disease (painful crisis).

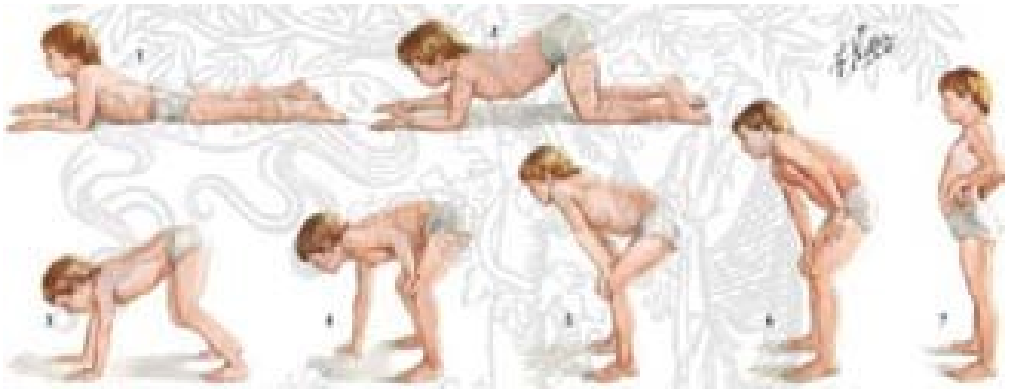
Pyruvate kinase deficiency (haemolysis not precipitated by drugs or infections).

Management

- ✓ Avoidance of precipitating factors.
- ✓ Gradually improve by age.

DUCHENNE MUSCULAR DYSTROPHY

X Chromosome, Gene DMD, Location X p21-21.1



Gower's sign, climbing his legs when in standing up.

Incidence: 1/4000 boys.

- Muscular degeneration, progressive muscular weakness of legs, pelvis, loss of muscle mass, intact sensation, weakness spread to arms, neck, other areas of the body.
- By age 12 years most patient are wheel chair dependent associated with skeletal deformities, intellectual impairment.
- Average life expectancy is around 25 years.

Investigations

- ✓ Muscle biopsy.
- ✓ DNA studies.
- ✓ Rise of serum creatine kinase, creatine phosphokinase, and serum aldolase.
- ✓ Nerve conduction velocity (EMG).

HEMOPHILIA A

X Chromosome , Gene F 8 , Location X q 28

Impairment of body ability to control blood clotting, stopping ble-ed when blood vessel is broken, due to deficiency of Factor VIII.

Incidence: 1 / 5000 male Births.

- Mild haemophilia: F VIII 5 - 50 % of normal.
- Moderate haemophilia: F VIII 1 - 5% of normal.
- Severe haemophilia: F VIII less than 1% of normal.

Internal bleeding usually occur when F VIII level is less than 5%

Clinical picture

- 70 % of cases not bleed from circumcision during 1st year of life.
- Child is easily traumatized, bruising especially in knees, elbows when baby start to crawl (6-9 months age).
- Repeated hemoarthrosis is common. Bleeding may be internal if FVIII < 5%, may cause damage to any internal organ and tissue, and may be life threatening.
- In neonatal period baby may presented with intracranial hemorrhage as FVIII does not cross placenta during pregnancy.

Investigations

- Normal coagulation profile except prolonged activated partial thromboplastine time (APTT) which measure the intrinsic pathway of coagulation (which includes

the common pathway + Factors I, II, V, X) + Factors VIII, IX, XI, XII , it rises to double N value.

- Low level of factor VIII is diagnostic.
- With Von Willebrand disease the Bleeding Time is prolonged (due to the associated thrombocytopenia)
- The mother of the child usually have low factor VIII (30-70%).

Management

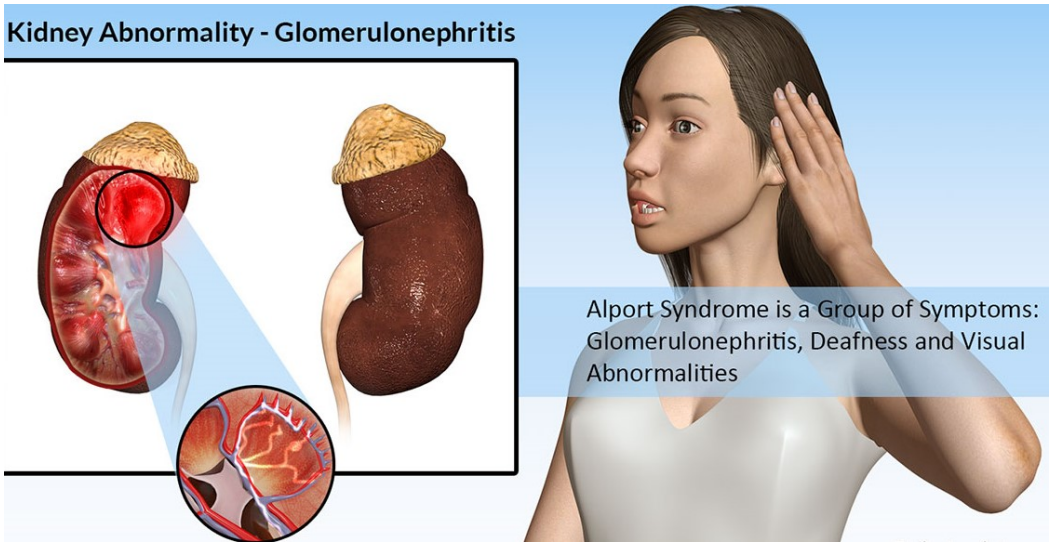
- ✓ Prophylactic measures for avoidance of trauma.
- ✓ In normal situations we aim to raise FVIII level to 30- 40 %, but with major operation we have to raise it to 100 %
- ✓ Fresh plasma, rise FVIII up to 5%, 10-20 ml /Kg /12 hours.
- ✓ Cryoprecipitate, rise FVIII up to 25% (contain FVIII 100 U + fibrinogen) 1 bag/5 Kg B.Wt.
- ✓ FVIII concentrate infusion, raise FVIII up to 100 %. Number of units desired to rise FVIII to the level needed ÷ 2 X B.Wt. (Kg). OR 20 units/Kg twice daily, each bottle of FVIII labelled with the number of units it contain.
- ✓ Post infusion level FVIII. No aspirin. No antihistaminics.
- ✓ Measuring FVIII antibodies, and 40 days to be passed between repeated FVIII transfusions or until all antibodies disappeared.

X Linked Recessive

ALPORT SYNDROME

X Chromosome, Gene COL 4 A 5 , location X q 22.3

Identified by British Physician.Ceciel Alport in 1927.



Alport syndrome

Incidence 1 / 5000 Births.

- Hereditary nephritis.
- Haematuria.
- Sensory neural deafness.
- Visual deterioration.
- Retinopathy.

WISKOTT ALDRICH SYNDROME

X Chromosome, Gene WAS, Location X p 11.22-p 11.23

Named after Paediatricians A Wiskott (Germany) &R.A. Aldrich(USA), in 1954

Wiskott Aldrich Syndrome

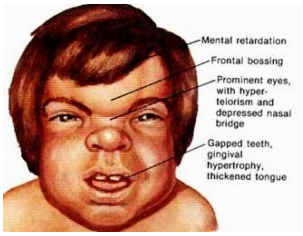
Incidence 1-10 / million male is worldwide.

- Low platelet (thrombocytopenia).
- Immune deficiency.
- Repeated infection.
- Eczema.

HUNTER DISEASE

X Chromosome , Gene IDS , Location X q 23

Named after Charles A. Hunter, Canada in 1917



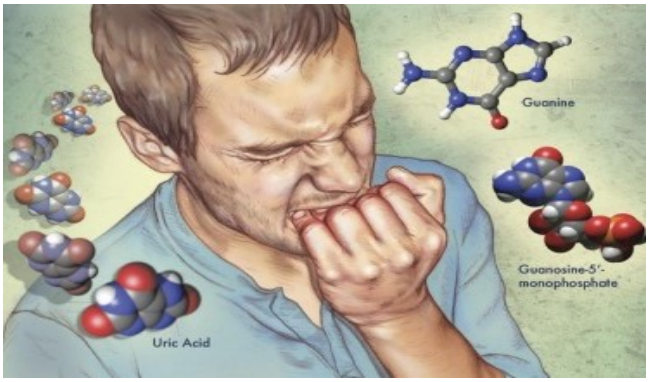
Incidence 1 / 162.000 Births .

- Mucopolysaccharidosis Type II, due to deficiency of enzyme id-uronate 2 sulfase required for the degradation of specific glyco-samilycans, its absence results in harmful accumulation of these substances in cells throughout the body.
- The disease is progressive and life-limiting disease, start to app-ear after the 1st year of life.
- Delayed milestones.
- Mental retardation.
- Large head, prominent forehead, fattened nasal bridge, and big tongue .
- Deafness.
- Visual disturbances.
- Joint stiffness, carpal tunnel syndrome.
- Frequent infection of ears and respiratory tract.
- Hepatosplenomegaly.
- Aggressive behaviour.

LESCH NYHAN SYNDROME

X Chromosome , Gene HPRT 1 , Location X q 26.2-q 26.3

Recognised in U.S.A. by medical student, Michel Lesch and his mentor paedia-trician Bill Nyhan who published their findings in 1964.



Lesch Nyhan Syndrome

Incidence 1/380.000 Births.

- Inborn error of metabolism result from deficiency of enzyme Guanine Hypoxanthine Phosphoribosyle transferase, causing accumulation of uric acid.
- Delayed milestones.
- Mental retardation.
- Self-destructive behavior resulting in self-mutilation through biting fingertips and lips (of unknown cause).
- Hyperuricemia, and severe gout.
- Uric acid urinary stones.
- Repetitive movement of arms and legs similar to those seen in Huntington's disease.

CHROMOSOMAL ANOMALIES

ANY CHANGE in the NORMAL STRUCTURE or NUMBER of CHROMOSOMES often results in PHYSICAL or MENTAL ABNORMALITIES.

DOWN SYNDROME (Trisomy 21)

Extra copy of chromosome 21, 47 XX + 21, Location 21 q 22.3

Named after British physician, John Langdon Down, in 1866.

Abnormality	AFP	hCG	µE3
Neural Tube Defects	↑	—	—
Trisomy 21	↓	↑	↓
Trisomy 18	↓	↓	↓

AFP (Alpha Feto Protein.

hCG (human Chorionic Gonadotrophine)

uE3 (unconjugated Estriol).

Incidence 1/700 Life Births, incidence increase with age.

- Presence of extra copy of chromosome 21(47 XX + 21).
- The commonest chromosomal anomaly, include three types,

Non-disjunction (95%). Translocation (4%), Mosaicism (1%).

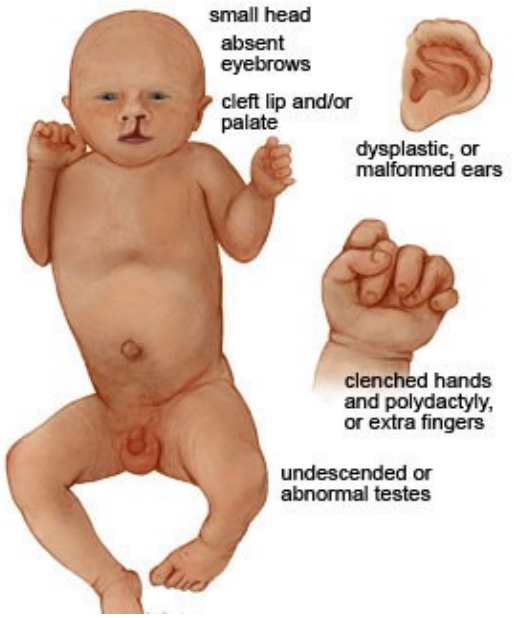
Clinical Picture

- Mental Retardation.
- Delayed milestones.
- Upper slanting eyes.
- Epicanthus fold.
- Brush field spots in iris.
- Depressed nasal bridge.
- Big tongue.
- Flat occiput.
- Single palmar and plantar creases.
- Rudimentary 5^{th} Finger.
- Gape between 1^{st} and 2^{nd} toes.
- Congenital heart (50% of cases VSD).
- Hypothyroidism in (30% of cases).
- Leukaemia (10 times more common).
- Intestinal obstruction.
- Hirschsprung`s disease.
- Usually associated with infertility.

TRISOMY 13 (Patau Syndrome)

Three copies of genetic material for Chromosome 13

First described by German born American geneticist, Klaus Patau in 1960



Trisomy 13 (Patau Syndrome)

Incidence 1/5000 Births.

- Mental Retardation .
- Microcephaly.
- Microphthalmia, and Visual impairment.
- Clenched hands with extra finger and / or toes.
- Cleft lip with or without cleft palate.
- Hypotonia.
- Brain anomalies, heart defect (V.S.D.or A.S.D.), renal anomalies.
- Neural tube defect.
- Undescended testes.
- Deafness.
- Survival beyond the first year is uncommon.

TRISOMY 18 (Edward Syndrome)

Extra copy of Chromosome 18, 47 XY +18, Location 18 p11.1-q12.1

Described by British medical geneticist R. Edward, in 1960

Trisomy 18 , "Edward Syndrome".

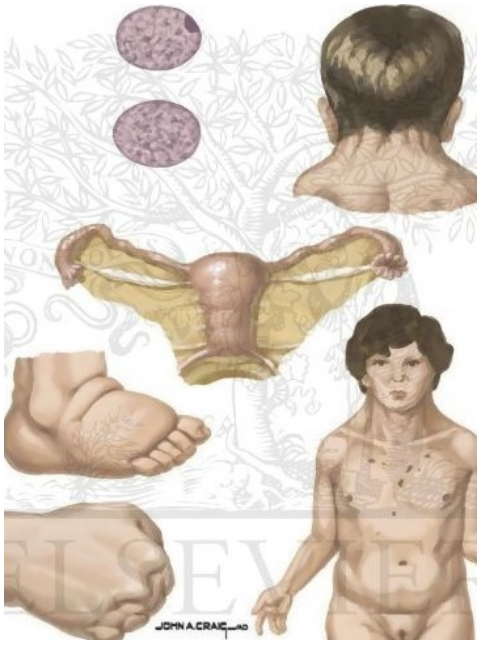
Incidence: the most common chromosomal abnormality after Down syndrome.

- Abnormal- shaped skull, and short neck.
- Small jaw, and mouth.
- Severe intellectual and physical defects.
- Delayed milestones.
- Dysplastic malformed low set ears.
- Shield chest, prominent sternum with wide set nipples.
- Clenched fists with overlapping of fingers.
- dysplastic malformed low set ears, shield chest, prominent sternum with wide set nipples.
- clenched fists, overlapping of fingers.
- Congenital heart defect.

TURNER SYNDROME (XO)

One of X Chromosome is missing , Gene SHOX

Named after Henery Turner, Endocrinologist, USA 1938



Characteristics of Tuner syndrome

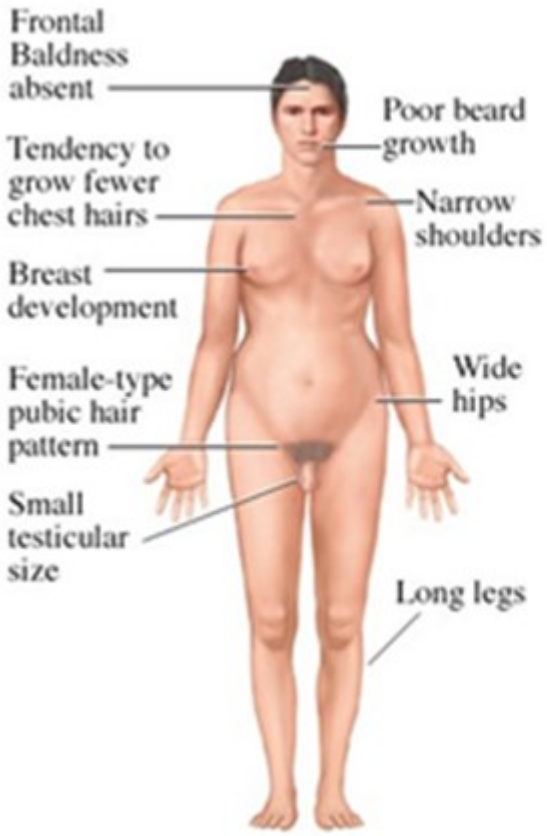
Incidence 1 / 2500 Live female birth.

- The most common female sex chromosome abnormality.
- Normal female external genitalia, uterus and fallopian tubes. Rudimentary ovaries, and primary amenorrhoea(infertility).
- Short stature, and webbed neck.
- Cubitus valgus.
- Shield shaped thorax, and widely spaced nipples.
- Low posterior hairline, and brown spots (Nevi) of the skin.
- Lymphedema of hands, and feet.
- Low seat ears.
- Small finger nails.
- Coarctation of aorta.
- Normal IQ.

KLINEFELTER SYNDROME

47XXY karyo type (mosaic 47 XXY /46 XY)

Described by American Endocrinologist, Harry Fitch Klinefelter, in 1942.



- **Lower IQ than sibs**
- **Tall stature**
- **Poor muscle tone**
- **Reduced secondary sexual characteristics**
- **Gynaecomastia (male breasts)**
- **Small testes/infertility**

Klinefelter Syndrome

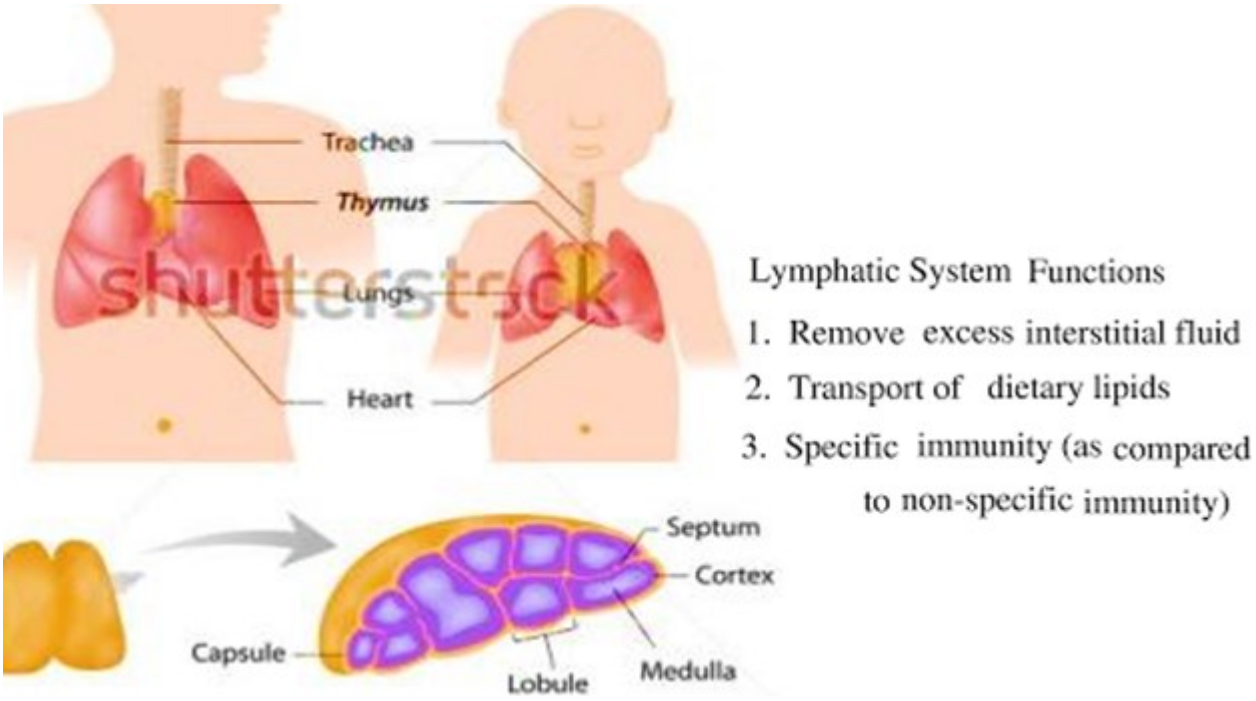
Incidence 1/ 500 Births.

- Become more evident during puberty.
- Tall Stature.
- Long Arms and Legs.
- Gynecomastia.
- Female type pubic hair pattern.
- Wide hips.
- Small firm testes, azoospermia, and infertility.
- Elevated level of gonadotrophins.

DI GEORGE SYNDROME

Deletion from chromosome 22, location 22 q 11.2

Described in 1968 by Italian American paediatric endocrinologist, A. DiGeorge.



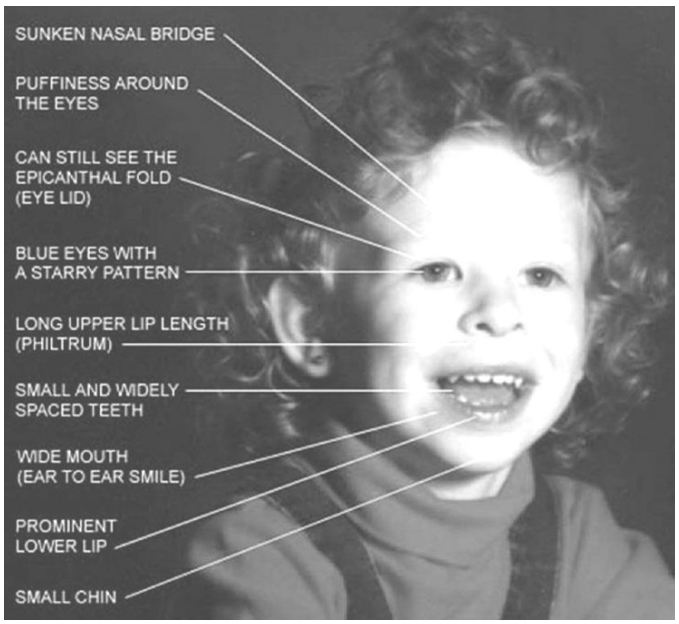
Incidence 1 / 4000 Births.

- The lost gene is normally required for development of thymus, immune system, and T cells.
- Poor immune system function.
- Recurrent infection.
- Heart defect, (commonly truncus Arteriosus).
- Cleft palate.
- Hypoparathyroidism.
- Hypocalcaemia.

WILLIAMS SYNDROME

Deletion of about 26 genes from chromosome 7, Location 7 q 11.23

Identified by Newzeland Cardiologist, John Williams, in 1961.



Williams Syndrome

Incidence 1/8000 Births.

☺ Unusually cheerful demeanour, and ease with strangers.

☺ Elfin like facial features, wide mouth, full lips.

☺ Delayed milestones.

☺ Mental retardation.

☺ Widely spaced teeth, long philtum, small chin.

☺ Flattened nasal bridge, and small upturned nose.

☺ Hypercalcaemia, and Supravalvular aortic stenosis.

☺ Hyperacusis (sensitive hearing).

☺ Hypothyroidism.

☺ Early puberty.

ANGELMAN SYNDROME

Deletion of Chromosome 15, Location 15 q 11.2 – q 13

Named after British, Paediatrician, Harry Angelman, in 1965

Angelman Syndrome

Incidence 1 / 10.000 - 20.000 Births.

☺ Primarily affects the nervous system.

☺ Hyperactivity, and short attention span.

☺ Happy, excitable, demeanour, with, frequent smiling ,laughter.

☺ sleep disturbances.

☺ Hand flapping movement.

☺ Seizures.

☺ EEG gives characteristic pattern (large amplitude slow spike waves).

PIERRE ROBIN SYNDROME

Chromosome 17, Location 17 q 24.3-q 25.1

Named after the French Dental surgeon Pierre Robin, in 1860

Pierre Robin Syndrome

Incidence 1 / 10.000 Births

- ∅ Microcephaly.
- ∅ Microphthalmia.
- ∅ Microganthia.
- ∅ Glossoptosis, backward displacement of tongue which may cause closure of throat and obstruction to the air passage during respiration.

∅ Most of cases suffer from cleft palate, but none of them has cleft lip.

CRI DU CHAT SYNDROME

Deletion of short arm of chromosome 5, Location 5 p 15.2

Described by French, Geneticist, Jerome Lejeune, 1963

Cri Du Chat syndrome

Incidence 1 / 50.000 Births.

- Mental retardation.
- Delayed milestones.
- Hypotonia.
- Microcephaly, and round face,
- Microganthia.
- Microphthalmia.
- Hypertelorism .
- Epicanthus fold.
- Low set ears.
- High-pitched cat like cry is characteristic .
- Renal or cardiac anomalies.

PRADER WILLI SYNDROME

Deletion of long arm of chromosome 15, Location 15 q 11.2

Described by, Swiss Endocrinologists, Andrea Prader, and Heinrich Willi, in 1956

Prader willi syndrome

Incidence 1 / 10.000 Births.

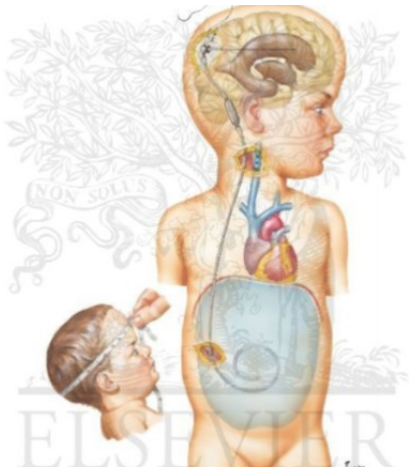
- Mental Retardation.
- Almond shaped eyes.
- Short stature.
- Small hands and feet .
- Unstoppable appetite.
- Morbid obesity.
- High tendency for type II diabetes mellitus.
- Hypotonia.
- Hypogonadism, and Infertility.

MULTIFACTORIAL DISORDERS

Conditions or diseases arising from combination of GENETIC and NON- GENETIC causes, including ENVIRONMENTAL FACTORS.

HYDROCEPHALUS

Chromosome 3, Gene Location 3 q 22 - q 24



Ventriculo Peritoneal Shunt

Incidence 4/1000 Live Births

- Congenital stenosis/obstruction of aqueduct of Sylvia's, foramen of Oval, or foramen of Magendi.
- Normally choroid plexus produce 750 ml CSF daily.
- The defect may be in excess production of CSF, or in its reabsorption, or 2^{ry} to intracranial hemorrhage, or choroid plexus papilloma, or tumor or meningitis.
- Progressive ↑ in head circumference, bossing of head, wide fontanels, wide separation of sutures, sun
- sitting eyes, cracked pott sign and may result in M. Retardation.
- Transillumination using fibroptic light.
- X ray skull, CT scan brain.
- TORSCH screening.
- Ventriculoperitoneal shunt (common) or Ventriculoatrial shunt.

CONGENITAL TALIPES EQUINOVARUS (Club Foot)

Chromosome 5, Gene PITX 1, Location 5 q 31.1

Incidence 1 / 500 Births (50% of cases are bilateral).

- The most common birth defect.
- More common in males.
- Normally the neonate can touch leg with small toe, and straight line can pass from the heel of feet to 2nd toe.
- May be Positional, or Structural.
- Positional: no restriction of passive movements of ankle joint.
- Structural: very restricted passive movements of ankle joint.
- Management: casting.

HARE LIP AND/OR CLEFT PALATE

Chromosome 1, Gene IRF 6, Location 1 q 32 - q 41

Hare Lip before and after surgery

Incidence 1 / 700 Births.

- ☺ Hare Lip results from failure of fusion of medial nasal and maxillary processes at 6-8 week gestation.
- ☺ Cleft palate results from failure of primary palatal processes to fuse at 7-12 wee-ks gestation.
- ☺ Each one may be unilateral or bilateral, and may be combined.
- ☺ First operation when baby 10 pounds, and thrive for correction of hare lip.
- ☺ Second operation at age one year before starting speech for correction of cleft palate.
- ☺ small hare lip may treated by T-shaped strapping which may be effective.
- ☺ Baby susceptible to aspiration pneumonia.
- ☺ Showing the parents a picture of such condition before and aft-er operation is helpful for reassurance.
- ☺ Needs team approach, and speech therapist.

EXOMPHALOS (Omphalocele)

Chromosome 2, Gene Location 2 q 31.1

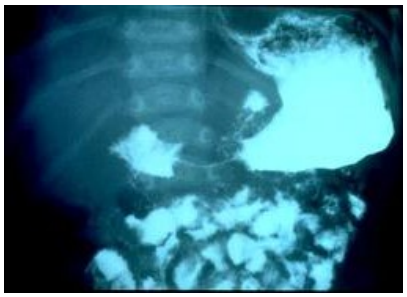
Incidence 1/5000 live births.

- Abdominal wall defect at the base of umbilical cord, infant born with sac protr-uding through the defect which contain small intestine, liver, large intestine, sac attached in its centre to the umbilical cord, and it turned black in color after a while.
- Considered surgical emergency, primary consideration is infect-ion, and drying of the contents.
- Cover with warm, moist, sterile dressing.
- Nasogastric tube to keep stomach empty.
- Surgical intervention as soon as infant is suitable.

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

Described by Hirschsprung in 1888

Olive mass, peristaltic waves



Barium meal X ray: String Sign.

Incidence

1/5000 babies, ♂ in boys, start to appear on 2nd-3rd week of life.

- One of most common gastrointestinal disorders in early infancy.
- Hypertrophy of circular muscles of pylorus results in constrict-ion and obstruction of gastric outlet.

Diagnosis

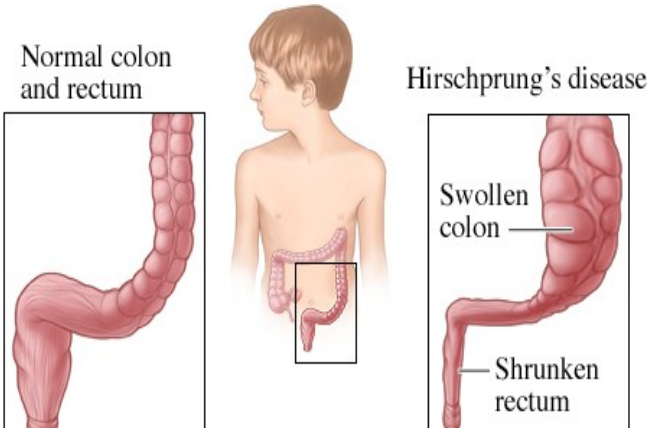
- Projectile vomiting after feeding.
- Dehydration, and metabolic alkalosis.
- peristaltic movements from left to right, small olive shaped mass in epigastrium or under the liver.
- Feeding test: diagnostic.
- X ray abdomen:erect/supine -double buble appearance .
- Barium meal: string sign.
- Abdominal sonar: diagnostic.

Management

- I.V. fluids, correction of dehydration, and metabolic alkalosis.
- Surgical: Rammstdt operation.

HIRSCHSPRUNG`S DISEASE (Aganglionic Megacolon)

Chromosome 10, Gene location 10q11.21, MIM number 142623



Incidence: 1/5000 livebirth.

The most common chromosomal abnormality associated with HSCR is Down syndrome which occurs in 2-10 % of individuals with HSCR.

Clinical Picture

- Constipation.
- Abdominal distension.
- Projectile vomiting.
- Bile stained vomitus.

Diagnosis

- ✓ Per-rectal (PR) examination: small empty rectum, hard stool above and explosive passage of flatus and stool.
- ✓ Plain X ray: multiple fluid levels.
- ✓ Barium enema: characteristic transitional zone, funnel shaped separate normal mucosa(above) from aganglionic segment.
- ✓ Manometric studies: using special balloon.
- ✓ Rectal suction biopsy: diagnostic.

Management: surgical.

IMPERFORATE ANUS

Incidence: 1 / 5000 live births.

- The baby develops this defect or abnormality during the fifth to seventh weeks of the mother's pregnancy.
- Malformation of the anorectal region.
- Include wide spectrum of abnormalities, either supra, infra,or intermediate to the levator ani muscles (pelvic floor) which is taken as landmark.
- The rectum may end by blind pouch that does not connect with the colon or may have opening to bladder, urethera, or vagina.

Clinical picture

- Absence or misplaced anal opening, or anal opening very near to the vaginal opening in the female.
- No passage of stool within 24-48 hours after birth.
- Stool may passed through vagina or urethera.
- Abdominal distension.

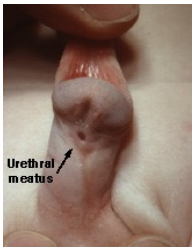
Investigations

Coin shadow X ray, to localize the site of obliteration.

Management

Surgical correction.

HYPOSPADIAS



Incidence: 1/300 live male.

- Varies in severity, in most cases, the penis opening located near the tip at the penis in the glans (bulb).
- More severe form occur when the penile opening at mid shaft or base of the penis and occasionally in the scrotum or perineum (underneath scrotum).
- Often associated with chordee, tight fibrous band that results in a downward curvature of the penis seen with penile erection.

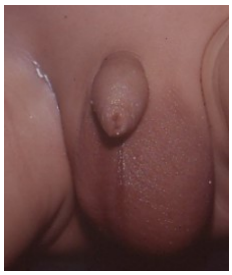
Clinical picture

- The meatus occurs on the under surface of the penis, usually associated with three features:
  - Ventral meatus.
  - Ventral curvature (chordee).
  - Dorsal “hood” deficient foreskin ventrally, and child has to sit down to void.

Management

- ✓ Infant with hypospadias should not be circumcised
- ✓ Most urologists recommend repair before 18 months of age.

CONGENITAL HYDROCELE



Definition

- Accumulation of liquid in scrotum between visceral and parietal layers of tunica vaginalis, due to persistence or delayed closure of processus vaginalis of testis.
- Clear serous fluid, transilluminating mass in one or both sides, fluid is squeezed into scrotum during birth and known as hydro-cele which usually disappears within few months, presence of frequent erections are common.
- May be communicating, hydrocele of the cord, or abdomenoscr- otal hydrocele.

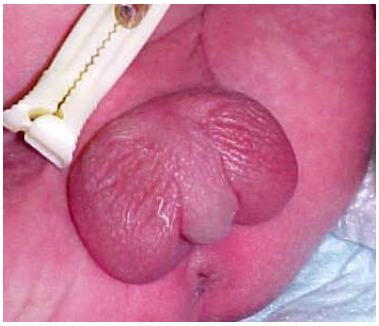
Clinical picture

- Cystic swelling.
- Non tender.
- Transilluminating.
- Can get above swelling, and testis not palpated.
- often associated with inguinal hernia.

Management

surgery indicated if spontaneous resolution not occur by age 1 yr.

DISORDER OF SEX DEVELOPMENT (DSD)



Incidence: 1/4000 infants.

hermaphroditism can be caused by translocation of a segment of the Y chromosome containing the SRY gene (480000; Yp11.3) to the X chromosome.

Types

- 46,XXDSD (virilzed female): female genotype 2 ovaries, external genitalia show variable degree of virilization.
- 46,XYDSD(undervirilzed male): male genotype 2testes,external genitalia show variable degree of feminization.
- 45,X/46,XY mosaicism (true hermaphroditism): range from nor-mal male to normal female phenotype, both ovaries and testes present.
- Complete Gonadal Dysgenesis (CGD): either pure CGD (testes or ovaries) or mixed CGD (testes and streak gonad).

Causes

- Congenital adrenal hyperplasia.
- Placental aromatase deficiency.
- Ovarian tumour.
- Maternal hyperandrogenic condition.
- Enzyme defect in testosteron synthesis.
- Defect in testosteron metabolism.

- Endorgan resistance to testosteron.
- Maternal drug ingestion: finasteride, spironolacton, phenytoin.
- Complete gonadal dysgenesis.

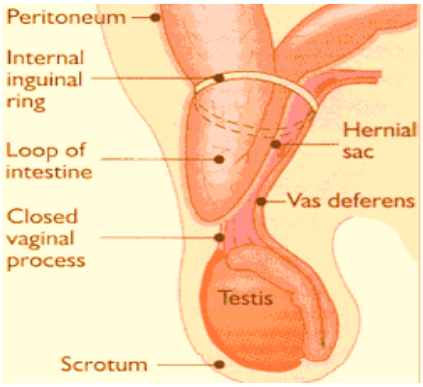
Investigations

- Ultrasonography/MRI for sex determination.
- Chromosomal study.
- Gonadal biopsy.
- Hormonalstudies: testestrone, DHT, FSH, LH, 17-hydoxypregne-nolone ,11dexycorticosterone, plasma renin activity, serum electrolytes.

CONGENITAL UMBILICAL HERNIA

- Seen in 10% of infants.
- More common in black child.
- Affecting boys more than girls.
- Resolve without any treatment by age 2-3 years.
- Obstruction or strangulation is rare.
- Surgery necessary only if not closed after 4 years.

Congenital INDIRECT INGUINAL HERNIA



Incidence

30% of preterm infants < 1000 gm

5% of preterm infants < 1500 gm

- Protrusion of whole or part of intestine through processus vaginalis.
- More common in males.
- In females the ovary is often in the sac.
- May be :
  - Reducible.
  - Irreducible.
  - Obstructed .
  - Strangulated.
  - Inflamed.

Management

Inguinal hernia repair is the most common operation performed in the preterm infants.

Congenital CRYPTORCHIDISM

Incidence: 5% in fullterm boys & 1% in 1 year old boys.

- Most common genital problem in paediatrics.
- Commoner in preterm, and small for date.
- Failure of intra abdominal testis to descend into scrotum.
- Either absent, ectopic, retractile (can manipulated into srotum).
- May be unilateral (80%), or bilateral (25%).
- Testis often palpable within inguinal canal.
- Non palpable testis occur in 20%, and 20-40% of non palpable testis, the testis are absent on surgical exploration.
- 90% of untreated males with bilateral absence develop azospe-ermia, and their risk of neoplasia is 3%
- Commonly associated with Prad-der Willi, Kallmann, Laurence Moon Biedl syndromes.

Diagnosis

θ Clinical examination.

θ Ultrasonography abdomen and pelvis.

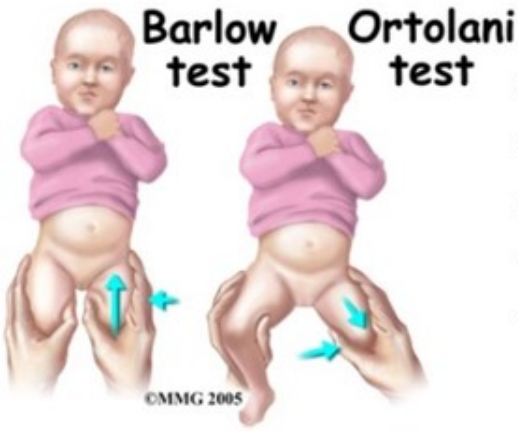
Management

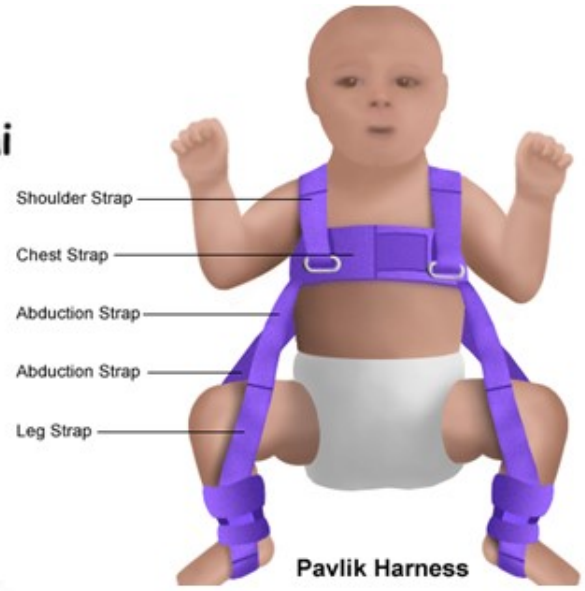
➢ Surgical consultation at age 6 months.

➢ Operation usually by age 1 yr, orchidopexy if testis is felt in ing-uinal canal or below (not retractile), orchidectomy if atrophic intraabdominal testis detected especially after puberty for high risk of malignancy.

Congenital HIP DISLOCATION

Chromosome 13, Gene Location 13 q 22





Incidence 1/1000 Babies.

- Common in female.
- Common breech presentation.
- Asymmetry of both inguinal ligaments.
- Incomplete abduction of thigh in the affected side.
- Difference in the length of both lower limbs.
- May be unilateral or bilateral.

Differentiation from sub-laxation of hip

With sublaxation of hip:

- No feeling or hearing click,clunk, or jerky movement of hip joint
- The femur head is within acetabulum.
- No asymmetry of inguinal ligaments.
- Only we detect excessive movement of femur head.

Diagnosis

- Ortolani`s Test :bilateral abduction of both thighs together with pushing greater trochanter using middle finger to feel a click.
- Barlow`s Test : fixation of one side in abduction position and move the other with pushing lesser trochanter to outside using big finger to feel click + clunk + jerky movement.
- Plain X ray hip joint: not conclusive before age 4 months when ossific centre of femoral epiphysis appear.
- Ultrasonography of hip joint: conclusive test by detection of $\propto$, β angles during the static, and dynamic state of hip joint.
- Early diagnosis and treatment are important, routine screening for every neonate after birth.

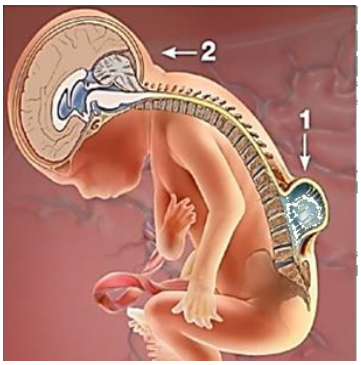
Management

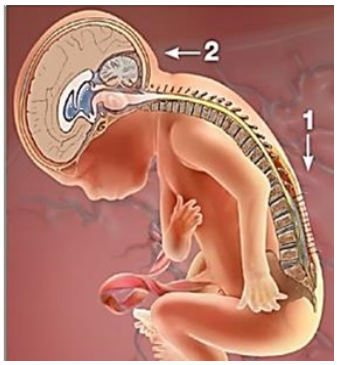
Fixation from age 2 weeks, for period of 2-3 months, using:

- Pavlik harness.
- Van Rosen cast.
- Aberden cast.

NEURAL TUBE DEFECT (Spina Bifida)

Chromosome 6, Location 6 q (T Locus)





Myelomeningocele,before and after operation in utero

sacral sinus and dimple

Incidence: 1 / 2000 Births.

Commonly arise from the Lumbosacral region.

Include Spina bifida occulta and Spina bifida manifesta.

Spina bifida occulta: mid defect of vertebral Bodies, presence of dimple, dermal sinus, lipoma, or tuft of hair in lumbosacral region, discoloration of skin. Occasionally associated with Diastematomyelia, Syringomyelia, and Tethered Cord. X-ray shows failure of closure of vertebral bodies (fusion), and most cases develop hydrocephalus later.

Spina bifida manifesta

- Meningocoele: bone defect with herniation of meninges & intact overlying skin.
- Myelomeningocele: both meninges and spinal cord protrude through skin defect.
- Encephalocele: bone defect of skull with herniation of meninges and brain tissues

Myelomeningocele

Encephalocele

Lacunar skull: common with NTD as multiple low density areas of skull.

Clinical picture

- Usually associated with severe physical, and mental disabilities.
- Paralysis of both lower limbs, or quadriplegia.
- Incontinence of stool, and urine.

Prenatally diagnosis

- ✓ ↑ alpha-fetoproteins in amniotic fluid.
- ✓ Ultrasonography.

Management

Surgical correction within the 1st few days, selection of cases depend upon the number of affected vertebrae, presence or absence of paralysis of lower limbs, loss of sensation of lower limbs, incontinence of urine or stool, presence of associated congenital anomalies (VACTERL) in addition to the religious, economic factors.

ANENCEPHALY

Incidence: 1 in 670 births.

- Couples that have had a previous child with a NTD have 1 in 40 chances of recurrence.
- More distant (second degree) relatives to an individual as nices, or nephews would have 1 in 200 risk of a NTD.
- Third degree relatives such as cousins have a 1 in 400 risk.

- Fourth degree would have a risk similar to general population.
- Anencephaly is seen 5 times more often in females than males.

Infant fail to develop a normal head and brain structure, as result of failure of the neural tube closure at the 3rd - 4th wk pregnancy.

Causes

- Folic Acid deficiency.
- Hypervitaminosis A.
- Undiagnosed diabetes.
- Environemental/chemical exposure.

At Risk

- Women taking anticonvulsant medication.
- Woman with undiagnosed or uncontrolled diabetes mellitus.
- Any woman with a family history of NTD.

Suggested screening test

- It is common to screen women`s blood for alpha fetoproteins, (protein produced by the fetus that is excreted into the amniotic fluid).
- Abnormal level may indicate brain defect or NTD.
- Amniocentesis can help detect NTD by measuring AFP.
- There is no cure or standard treatment for this birth defect.

Prevention

Tacking 4-5 milligrams of folic acid daily for 2-3 months before conception for all woman at risk or having a child with NTD.

Autism

Chromosome 2, Gene Location 2 q 31.1

Incidence 10 / 1000 Children.

- 4 times more prevalent in boys.
- No known racial, ethnic, or social boundaries.

- Very complex, often baffling developmental disability
- First described by Leo Kanner in 1943 as *early infantile autism*

  "Auto"-children are "locked within themselves."
- For next 30 years, considered to be an *emotional disturbance.*
- Very likely **neurological** in origin- not emotional, not the refrigerator mom.
- Autism impacts normal development of the brain in areas of **social interaction** and **communication skills.**
- Difficult to communicate with others and relate to the outside world.
- **Unusual responses to people.**
- Lack of expression and communication with others.
- **Attachment to objects.**
- **Resistance to change in routine,** and never say " i ".
- Lack of emotion with others-masked face.
- May exhibit **repeated body movements:** hand flapping, rock-ing, abnormal movements, and habits.

- Compulsive behavior.
- Echolalia and language problems.
- ↑ tolerance to painful stimuli.
- Occasionally, aggressive and/or self-injurious behavior may be present.
- Epilepsy is common to occur.

Locked within themselves , and a young boy with autism who has arranged his toys in a raw (compulsive behavior).

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